HANS FORSSMAN

ON HEREDITARY DIABETES INSIPIDUS

WITH SPECIAL REGARD TO A SEX-LINKED FORM

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ON HEREDITARY DIABETES INSIPIDUS

FROM THE MEDICAL CLINIC OF THE UNIVERSITY OF UPSALA, SWEDEN
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AND
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ON HEREDITARY DIABETES INSIPIDUS

WITH SPECIAL REGARD TO A SEX-LINKED FORM

BY

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Translated by Carolyn Hannay-King

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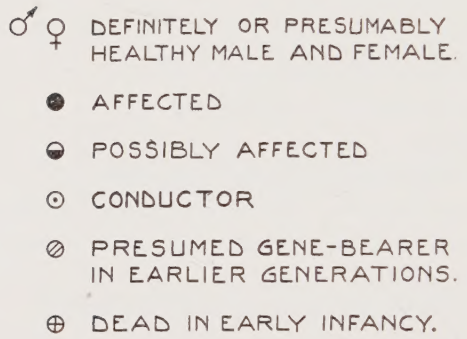
Symbols and abbreviations.



In fig. 1 certain symbols are used, that are given beside the figure.

The symbol for »conductor» is used not only for the females in the pedigrees showing sex-linked inheritance, but also for phenotypically normal gene-carriers in pedigrees with autosomal heredity.

A heavy line denotes the hereditary course of the disease in the pedigree.

In the notations of the type A: V: 8, the letter denotes a pedigree or a branch of a pedigree, the Roman figure generation, and the Arabic figure individual within the generation.

N. P. N. = non protein nitrogen.
S. r. = sedimentation rate (of red blood corpuscles).
D. i. (in tables, Case Histories and Bibliography) = diabetes insipidus.
I. U. = international unit.
Ecg = electrocardiogram.

Preface.

The present work is built upon 5 pedigrees with a total of 83 known carriers of diabetes insipidus genes, who have been traced by a genealogical investigation, covering about 5,500 subjects. The genetics of the disease will be discussed on the basis of this and earlier published materials. Some clinical results will be submitted, above all concerning symptoms in heterozygotes, on the appearance of diabetes insipidus in connection with pregnancy in female heterozygotes, and further more on the effect of posterior pituitary extract in cases from different pedigrees.

A patient treated at the Medical Clinic of the University of Upsala formed the starting point of the work and it is at this Clinic that most of the patients have been investigated. It is my pleasant duty warmly to thank the Head of the Clinic, Professor Gustaf Bergmark, for the interest and helpfulness he has shown me in every respect during many years.

When making statistical calculations I have been assisted by the staff of the Swedish State Institute for Human Genetics and Race Biology. I beg to tender my hearty thanks to the Chief of the Institute, Professor Gunnar Dahlberg, for allowing me to work at the Institution and for his great helpfulness in giving me advice and directions in questions of genetics.

The extensive genealogical work has been carried out by the Genealogical Bureau at Upsala. I wish to express my gratitude to the Chief of the Bureau, Miss Ella Heckscher, and to her assistant, Mrs Ella Littmarck, for their great interest, that has extended far beyond the professional routine.

My thanks are also due to the diabetes insipidus patients and their relations, without whose kind cooperation the

investigation would have been impossible; to nurses at the Medical Clinic for their generous help with water metabolism tests, often with great sacrifice of time; and to numerous colleagues for information about patients and for placing hospital records at my disposal.

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Upsala, March 1945.

Hans Forssman.

CHAPTER 1.

Review of the literature.

The literature on diabetes insipidus is extensive — indeed, in view of the rarity of the syndrome, we might say very extensive. The explanation is that this disorder has long presented, and still does present, unsolved problems. Although the survey below is in no way intended to be complete, it has become rather large. The author had the following motives for a relatively full review of certain parts of the literature: Earlier surveys of hereditary diabetes insipidus are coloured by the prevailing view that the disorder is only inherited by simple dominance. As it has now become clear that there are other modes of inheriting it, the literature should be examined anew. The problem of diabetes insipidus and pregnancy has not been satisfactorily treated since the research into the diuresis-promoting principle of the anterior pituitary lobe placed this question in a new light.

Definition. Frequency. Classification.

As is known, diabetes insipidus is characterized by large outputs of urine and heavy thirst, despite there being no sugar in the urine and no signs of renal disease. It is customary to speak of polyuria when the daily output of urine exceeds 2000 cc. Naturally, the condition must be of a certain duration to be denoted diabetes insipidus.

The disease is uncommon. Fitz (1914) collocated the materials from 4 hospitals and found 79 cases of diabetes insipidus in 553,077 patients treated — i.e. 14.5 cases in 100,000. Rowntree (1924) has, from the Mayo Clinic, collected 56 cases

among 428.000 patients. In statistics over 1 million patients from different places, including those in the Mayo material, he found 160 cases, i.e. 16:100.000. If all the patients in these materials had gone to the respective hospitals for other diseases than diabetes insipidus, these figures could be taken to express the true frequency of the complaint; naturally, however, it was for this very trouble that a number went to the hospital at all. For this reason the frequency ought to be less than the above figures. On the other hand, a slight or moderate diabetes insipidus could be overlooked even in a patient treated in hospital — in the present author's material this has happened several times. Such oversights, then, may also have lowered the figures published by Rowntree and others.

It has long been customary to differentiate between symptomatic and idiopathic diabetes insipidus, the latter group then embracing the definitely hereditary cases and such whose etiology is unknown. The symptomatic cases can be referred back to some other disease: cranial trauma, syphilis, tumour, encephalitis, etc. Needless to say, later developments or autopsy findings may relegate to the symptomatic group a case previously taken to be idiopathic.

Patho-physiology.

Polyuria by cerebral puncture.

The idea of an intercranial cause of disturbances of the water metabolism first arose from Claude Bernard's famous piqûre. Polyuria and an enhanced excretion of NaCl, both of an acute kind, can be induced by lesion to the bottom of the fourth ventricle (Claude Bernard 1855, Eckhard 1869 and 1872, cit. Kahler, Kahler 1886, Jungmann and Meyer 1913). The ways in which the effect is produced have not been worked out (Ellinger 1929). There is no simple way of linking up these observations on so-called puncture polyuria with what is otherwise known about the nervous-hormonal regulation of the water metabolism. More recent research into diabetes insipidus has completely passed over the puncture polyurias.

The posterior lobe system.

At the end of the 19th century, a number of clinical observations were advanced which supported the idea that the cause of diabetes insipidus was to be sought in or near the hypophysis. Diabetes insipidus was seen to result from cranial trauma (Kahler 1886), in connection with bitemporal hemianopsia (Kruse 1894), and in syphilitic basal meningitis (Oppenheim 1896). A classic case has been reported by Frank (1912), whose patient contracted diabetes insipidus as the result of a bullet wound in the head, X-rays being able to show the bullet to lie in the posterior part of the sella turcica.

It became clear that there was a connection between the syndrome of diabetes insipidus and the hypophysis when, in 1913, two investigators independently discovered that the symptoms could be effectively controlled by injection of extracts from the posterior pituitary lobe (von den Velden, Farini). The comprehensive literature on the pharmacodynamics of the posterior lobe extract has been reviewed in considerable detail by Schaumann in a survey of 1937. No exhaustive description is intended here; we will only establish a number of main points.

The water and salt content of the organism has proved of importance for the effect of the posterior lobe extract. There is little or no reaction to the hormone in individuals who are dried up, while the greatest effect is seen in water-loaded subjects (Motzfeldt 1924, Marx 1935). The human subject shows no clear effect from the extract when a given water loading has an NaCl content of about 1.5 % (Brunn 1920, McFarlane 1926, Adolph and Ericson 1927, and others). The addition of 10 % urea to the imbibed water also inhibits the effect even of large doses of posterior lobe extract (Samaan 1935).

The most important studies into the extract's point of action have been published by Starling and Verney (1925), and Verney (1926). These authors worked with a surviving heart-kidney-lung preparation, and showed that preparations of this kind produce an abundance of thin urine, comparable with that of the diabetes insipidus patients. When small quantities

of posterior lobe extract were added to the perfusion fluid, the amount of urine was very markedly lowered, and the concentration greatly enhanced. A dog's head was subsequently coupled to the rest of the apparatus, whereupon the diuresis was reduced and the concentration approached the normal, as when injections of posterior lobe extract are given. When a head was taken from a dog whose hypophysis had previously been extirpated, there was no antidiuretic effect, and the preparation continued to present the symptoms of diabetes insipidus. It was hereby demonstrated that a living hypophysis affects the kidneys by means of an exclusively humoral connection.

Denervation of the kidneys has proved to have no effect on their reaction to posterior lobe extract and water loading (Oehme and Oehme 1918, Verney 1929); nor do separation of the spinal cord at different levels or cutting of the nervi vagi (Janssen 1928) influence this reaction. By injecting the extract direct into the left renal artery, Miura (1925) was able to make the diuresis inhibition appear earlier on the left side than on the right.

In face of all these results, it seems indisputable that, even if other mechanisms may be thought included in the causal chain, the last link before the kidneys is nonetheless humoral.

The following remarks may be applied to the extract's point of action within the kidney. According to Poulsson (1930), the extent of the glomerulus filtration does not depend on the level of diuresis in the experimental animal. Bansi (1942) observed in normal human subjects a slight lowering of the glomerulus filtration when pituitrin was administered, and ascribed this to the influence of pituitrin on the glomerulus vessels. Burgess, Harvey and Marshall (1933) found that the glomerulus filtration in man and dog was as great during pronounced water diuresis as during an oliguria induced by posterior lobe extract. Walker, Pott, Oliver and McDowell (1941) found about 80 % of the water resorption to take place in the proximal tubule, without change of the osmotic pressure in the primary urine. They find it probable that only the water resorption in the

more distal part of the nephron, rendering the urine hypertonic in relation to the blood, proceeds under the influence of the hormonal anti-diuresis. This would explain why, even in severe diabetes insipidus, the daily output of urine does not usually exceed 20 litres, although the glomerulus filtrate amounts to about 150 litres per 24 hours.

Numerous clinical observations of diabetes insipidus attendant on injured or destroyed posterior lobes agreed with the view that the patho-physiological explanation of this complaint lay in insufficient or inhibited production of the anti-diuretic posterior lobe principle. In other cases of diabetes insipidus, however, the hypophysis was apparently quite intact. Marx (1941) enumerates 25 such human cases. A counterpart is found in a large number of results from experiments on animals, where diabetes insipidus had been induced by lesions not of the hypophysis but of the tuber cinereum or other parts of the hypothalamus (Camus and Roussy 1920, Houssay 1918, Leschke 1919, Bailey and Bremer 1921; and others).

The main contributors to the solution of this problem have been Ranson and his school, who in a series of studies investigated the anatomical and functional unit which they called the supraoptico-hypophyseal system. Using very circumscribed and exactly placed lesions, Fisher, Ingram, Hare and Ranson (1935) were able to induce a permanent diabetes insipidus in cats by bilateral lesion of the nerve fibres connecting the nucleus supraopticus with the posterior lobe of the hypophysis — the so-called tractus supraoptico-hypophyseos. On the other hand, all other parts of the cat's midbrain could be injured without giving rise to diabetes insipidus. Analogous experiments have also been made on other animal species: dog (Biggart and Alexander 1939), monkey (Magoun and Ranson 1939), guineapig (Gaupp 1941) and rat (Clark, quoted from Gaupp). An isolated injury to the tractus supraoptico-hypophyseos regularly resulted in secondary changes, both in the neuro-hypophysis and in the nuclei supraoptici. The nerve fibres in the pituitary stalk below the lesion became very much fewer, the posterior pituitary lobe atrophied, its net of nerve fibres grew thinner, the intermediate lobe wrinkled, and the

central lumen of the hypophysis became larger. Regenerative cell changes regularly arose in the nuclei supraoptici; extirpation of the posterior lobe was also followed by a marked atrophy of these nuclei. The observation confirms older studies by Mogilnitsky (1928), who saw changes after X-ray injury to the hypophysis appearing selectively in the nuclei supraoptici, and by Maiman (1930), who found atrophy in the same nuclei after lesions to the neuro-hypophysis.

There is no excluding the possibility that even other nuclei and their connections may, in different species of animals, play varying parts as main or accessory organs for the neurohormonal anti-diuresis. The discussion still proceeding round this matter has no bearing on the present author's problem, however.

Diabetes insipidus refractory to pituitrin.

It is known that a small number of cases of diabetes insipidus in man do not respond at all to treatment with posterior lobe extract (Elmer, Kedzierski and Scheps 1928, Biggart 1935, Falta 1938; and others). According to Biggart (1937), these refractory cases constitute between 5 and 15 % of the total number. That it is not merely a question of dosage has been shown by Falta (1938), who gave pituitrin to a refractory case every other hour, thereby reaching a high dose (unfortunately not defined) for the 24 hours, without getting any effect.

Veil (1923) has aimed at a division of diabetes insipidus into two clinical forms: a hyperchloremico-hypochloruric form and a hypochloremico-hyperchloruric form. According to him, the latter form is not affected by pituitrin. Veil's division has nowadays been generally abandoned, and in the same way, his observation of the connection between serum chlorides and susceptibility to pituitrin has been proved untrustworthy (Haymann and Fanconi 1926; Depisch and Högler 1927; and others). Karlson and Norberg (1936), who also criticized Veil's groups, suggest a division of the cases according to their reaction to pituitrin. An attempt to find the anatomical basis for resistance to pituitrin has been made by Biggart (1937). In 4 cases of 7 which reacted to pituitrin, the nuclei of the tuber cinereum

were intact, whereas these nuclei were engaged in 3 refractory cases. In view of this, Biggart sees the 'effectory path-way' of pituitrin in the tuber cinereum. This investigator points out himself the incompatibility of this hypothesis with the observation as to the effect of pituitrin on the isolated kidney. On the whole, the cases refractory to pituitrin cannot be fitted into the present-day view of the mechanism behind diabetes insipidus.

The investigations using experiments on animals have not brought us much further with this problem. The diabetes insipidus arising from lesion of the posterior lobe or its connections usually follows a characteristic course in 3 phases: a transitory polyuria, a short phase of normal diuretic level, and finally the phase of permanent diabetes insipidus (Biggart and Alexander 1939, Gaupp 1941; and others). According to Biggart and Alexander, the first transitory polyuria is refractory to pituitrin. It is still extremely uncertain how the different links in the 3-phase course are to be explained.

Wermer (1938), who induced diabetes insipidus in dogs by giving them extracts from the anterior pituitary lobe (see next section), found the symptoms to be refractory to pituitrin in one case, but to respond clearly to it in another.

The diuretic anterior lobe principle.

It has repeatedly been shown by experiment that total extirpation of the hypophysis never leads to permanent diabetes insipidus (Camus and Roussy 1913, Fee 1929, Richter 1934, Pencharz, Hopper and Rynearson 1936). Leschke (1919) has made a compilation of clinical material, showing total destruction of the hypophysis without diabetes insipidus. According to our present knowledge, the explanation of this long-puzzling fact is to be sought in the diuretic influence exerted by the anterior lobe of the hypophysis.

As early as 1909, Cushing, in a joint work with Crowe and Homans, advanced the idea of a diuretic principle in the anterior lobe.

In 1918 von Hann reported on 20 patho-anatomically investigated cases of diabetes insipidus, 3 of his own and 17

taken from the literature. In all these cases the posterior lobe of the hypophysis had been destroyed by the pathological process, whereas the anterior lobe was entirely or almost entirely intact. In the few cases where the anterior lobe was somewhat engaged, the intensity of the diabetes insipidus symptoms had fallen during the last few days of illness. Contrasted with these cases were 9 others, where both the posterior and the anterior lobe had been destroyed: in none of these cases could diabetes insipidus be demonstrated clinically. von Hann's conclusions deserve to be quoted word for word: 'Hypophysenerkrankungen rufen nur dann Diabetes hervor, wenn der Hinterlappen aus irgendwelchem Grunde, sei es durch einen Tumor, sei es durch entzündliche Prozesse zerstört oder schwer geschädigt wird, der Vorderlappen aber intakt oder zumindesten genügend funktionstüchtig bleibt'.

Nowadays the anterior lobe principle promoting diuresis is no longer merely hypothetical. During studies actually directed towards the growth hormone of the anterior lobe, Teel (1929) found that dogs given large daily doses of anterior lobe extract developed a polyuria and polydipsia which could in no way be distinguished from diabetes insipidus. The daily output of urine could increase from 750 to 7.000 cc. The effect did not appear until after 3—5 days' treatment with injections, and the symptoms did not disappear until some days after the administration of hormone had been discontinued. Teel's experiments have been repeated by Barnes, Regan and Bueno (1933), Biasotti (1934) and Wermer (1938). Schweizer, Gaunt, Zinken and Nelson (1941) have demonstrated the diuretic effect of anterior lobe extract in hypophysectomised rats.

Richter (1934) made an experiment which faithfully reproduced von Hann's observations on human material. The hypophysis was removed completely from 34 rats, and partially from 32. In no case did the total hypophysectomy lead to permanent diabetes insipidus. Of those animals undergoing partial hypophysectomy, 6 retained parts of the posterior lobe, in connection with the stalk. None of these 6 contracted diabetes insipidus. Permanent diabetes insipidus arose in 26 animals whose entire posterior lobe had been removed, but

whose anterior lobe had been partially retained. Richter has also observed that the diabetes insipidus following injury to the hypothalamus can only develop to its full extent when the anterior lobe is uninjured. By lesion to the hypothalamus of dogs, Keller, Noble and Hamilton (1936) induced a diabetes insipidus which, after it had been allowed to continue for 49 days, could be stopped by hypophysectomy.

Wermer (1938) has collected clinical evidence to support the existence of the diuretic anterior lobe principle. An example of such evidence is the oliguria in Simmond's disease, which disease is, as we know, caused by a more or less extensive destruction of the anterior lobe. Most patients with hypophyseal cachexia show a disturbance in the water metabolism which can be said to be the opposite of diabetes insipidus. They have no thirst — indeed, they may even be most anxious to avoid all fluid. A patient described by Marx (1941) had chosen to live exclusively on dry food, and had, in spite of constant body-weight, a daily output of urine of 120—180 cc, with a specific gravity of 1.032—1.036. Cases where the oliguria is not so extreme may also, on water loading, show a derangement with the same trend. The water test has an unusual course, with poor dilution and abnormally good powers of concentration, together with retention in the body of part of the quantity of water given (Marx 1928, Wermer 1938). Wermer takes the diuresis increase which appears in connection with pregnancy to indicate an increase of the diuretic activity of the anterior lobe.

The details of the way in which the diuretic anterior lobe principle works are far less clarified than those of the posterior lobe extract. Several investigations suggest that an indirect, perhaps an adenotropic, effect is in question. A circumstance primarily pointing in this direction is that the experimental anterior lobe diuresis does not begin until injections have been going on for several days, and only ceases several days after the hormone administration has been discontinued. Other investigations point direct at a connection with other ductless glands, above all the thyroid (Barnes, Regan and Bueno 1933, Biasotti 1934, Mahoney and Sheehan 1935, White and Hein-

becker 1937) and the adrenal cortex (Wermer 1938, Britton and Corey 1941). It is outside the province of this thesis to go into these investigations in a field of research which is under lively discussion, but which does not directly bear on the problems of the present author.

According to this account, the patho-physiology of the diabetes insipidus syndrome can be summed up as follows. The supraoptico-hypophyseal system regulates the formation of an antidiuretic hormone in the posterior lobe of the hypophysis. A lesion to this system in any of its three links (the nucleus supraopticus, the tractus supraoptico-hypophyseos or the posterior lobe) interferes with the circulation of the antidiuretic hormone. The effect of this substance on the kidneys is to raise the resorption of water in the tubules; when this effect ceases, a polyuria is set up, followed by a compensatory polydipsia. The polyuria which is set up can be regarded as the resultant of diuretic forces governed by the anterior lobe's diuretic influence (possibly via the adrenal cortex and the thyroid, perhaps via other ductless glands also, or in some other way) and is balanced by the inhibitory antidiuresis. Certain forms of diabetes insipidus may also be thought to arise when the function of the anterior lobe is enhanced, despite normal functioning in the posterior lobe system. A fact which deserves further stress is that the two components in this system of balancing powers are not equally matched. The effect of the antidiuretic hormone sets in within a few minutes, and is fairly transient. It produces the rapid changes in the diuresis neatly adapted to the different phases of the 24 hours covering the intake of nourishment, bodily movement, sleep, etc. The diuretic principle, about whose methods of functioning far fewer details are known, keeps the water diuresis constant at a certain level.

Diabetes insipidus and pregnancy.

Between diabetes insipidus and pregnancy there is a connection which reveals itself in different ways. Apart from casuistic reports, concise essays on this subject have been published by Kleinwächter (1898), Klaften (1927), Momigliano

(1929), Schellenberg (1930) and Henriet (1936). It has been customary to distinguish between the cases where pregnancy appeared in women previously suffering from diabetes insipidus, and those where the disturbance is contracted in association with pregnancy, the latter being called diabetes insipidus gravidarum.

As a rule, the syndrome in women suffering from hereditary diabetes insipidus becomes considerably more intense during the latter half of pregnancy, sometimes so much that the output of urine is doubled. Immediately after delivery the output of urine and consumption of water return to their habitual proportions (Adolf Weil 1884, Alfred Weil 1908, Jansen and Broekman 1921, Chester and Spiegel 1933, Ellermann 1939, Scherrer 1940, Mondt 1941, Gaupp 1941).

The diseases in the hypophysis and diencephalon involving symptomatic diabetes insipidus lead relatively often to regressive changes in the genital tract — in women to amenorrhœa and sterility (Skrobanski 1902, Leschke 1919, and others). It is therefore not unduly common for women with acquired diabetes insipidus to become pregnant. It is usual for those cases that, despite this fact, do become pregnant also to show an intensification of the disease from about the 4th or 5th month. This has been described in cases of diabetes insipidus with different, but in each case not conclusively hereditary, etiology, by Voituriez 1890, Chavane and Faure-Miller 1900, Skrobanski 1902, Ballerini 1921, Klaften 1927, Garretón 1927, Artaud 1933, Sferra 1938 and Vignocchi 1941.

In a case communicated by Brattström (1938), diabetes insipidus in a woman had arisen in direct association with a serious cranial trauma. Previous to the injury she had been through 2 pregnancies without any disturbance of the water metabolism. Her diabetes insipidus gradually subsided, but during a third pregnancy subsequent to this recovery, the symptoms recurred about the 7th month, to disappear again a few weeks after partus.

In a few cases it has been reported that the diabetes insipidus was not affected by the patient's becoming pregnant (Kölle 1926, Dellepiane 1934, Soule 1937).

Table 1.

Cases of diabetes insipidus gravidarum from the literature.

Authors	Publishing year	Pregnancy number	Symptoms first observed in	Cessation after delivery
Esterle (cit. from Kleinwächter)	1861	1 and 2	6th month	+
Benett (cit. from Duncan)	1868	1	5th »	+
Duncan a)	1888	5	6th »	+
b)	1888	1	6th »	+[1]
Dodd	1891	2	4th »	-
Vinay	1899	5	4th »	+
Janzen	1899	4—6	from the beginning	incomplete
Novak	1917	1—10	no information	incomplete
Gentili	1917	5	6th month	+
Gerloszy	1924	3	2nd »	no information
Gänsslen & Fritz	1924	1	no information	+[2]
Katz	1924	1—6	from the middle	incomplete
Stiglbauer	1924	2	5th month	no information
Fruhinsholz and co-workers	1928	4	from the beginning	incomplete
Mestiz	1930	1	7th month	+
Anselmino & Hoffman	1930	1 and 2	2nd »	+
Schellenberg	1930	2	9th »	+
Přibrský a)	1934	3 and 4	6th »	+
b)	1934	1	2nd »	+
Dietel	1935	1	6th »	+
Bleakley	1938	1	5th »	no information
Merlino	1938	1	2nd—4th month	+
Carter	1940	1	from the beginning	incomplete
Vignocchi	1941	1—9	5th—6th month	+
Pardini	1941	1—5	no information	+
Hart & Breiman	1941	1	6th month	+
Mondt	1941	1 and 2	from the middle	+

[1] no relapse in two subsequent pregnancies.
[2] „ „ „ one „ pregnancy.

There are also a few reports of a decrease in the intensity of the diabetes insipidus syndrome in connection with pregnancy (Merbach 1888, Vinay 1899, Duvoir, Pollet and

Cachin 1932). In the case described by Duvoir *et al.*, there was a mitigation of the diabetes insipidus in each of 3 separate pregnancies, the complaint again becoming worse after partus. The case was complicated with diabetes mellitus and great obesity.

Quite a number of cases have been communicated where diabetes insipidus was first contracted in association with pregnancy. 27 cases of this kind have been collected from the literature in table 1. In 17 of these cases the phenomenon occurred at the very first pregnancy, in 3 cases it was first observed in the 2nd pregnancy, 2 cases in the 3rd, 2 cases in the 4th, and 4 cases not until the 5th. Of the women who had already had diabetes insipidus gravidarum once, 11 subsequently went through one or more pregnancies, making a total between them of 35. In 32 of these pregnancies (9 women) there was a recurrence of diabetes insipidus; only 3 (2 women) proceeded with no recurrence. Janzen (1899) has noted a tendency in the disease to recur with enhanced intensity in subsequent pregnancies.

It is necessarily difficult to pin down the point in time when the pathological thirst becomes noticeable, as the complaint develops insidiously. The table shows that only a few of the women registered their increased thirst as early as the beginning of pregnancy; most of them noticed it in the middle, during the 4th to 6th months. Merlino (1938) describes how the symptoms manifested themselves weakly in the 2nd month, but grew in intensity from the 4th. The last weeks of pregnancy are usually the worst. In one case (Schellenberg 1930) the symptoms did not appear until the 9th month.

Just as the intensified permanent diabetes insipidus of pregnancy returns to habitual proportions soon after partus, so does the diabetes insipidus gravidarum begin to disappear immediately partus is over — in Příbrský's case (1934) as early as the beginning of labour; otherwise one of the first days of the puerperium. After one week the daily output of urine is often wholly normal. In other cases there is a rapid improvement, but a complete return to normal takes several weeks. In other cases, again, there is never any complete

return: the diuresis and water consumption remain somewhat higher permanently.

Transitory diabetes insipidus has also been observed by Lévy-Solal (cited from Henriet 1936) in a molar pregnancy. In one of Příbrský's (1934) cases, diabetes insipidus appeared for the first time in association with the extirpation of a tumour of the adnexa, disappeared about a month after the tumour had been extirpated, and subsequently recurred in connection with 2 pregnancies.

Diabetes insipidus gravidarum has been mentioned three times in connection with hereditary diabetes insipidus. Gänsslen and Fritz (1924) described the following strange case: A healthy woman married a man with diabetes insipidus, who belonged to a family that had a dominantly inherited form of the disease. The woman herself was healthy, and as far as is known there were no diabetes insipidus genes in her family. During her first pregnancy she became so intensely thirsty that she appeared to have contracted her husband's disease. When born, the child had diabetes insipidus. The phenomenon was not repeated in a later pregnancy; this time the child was healthy.

Marinesco (1895) published a case of 2 brothers with diabetes insipidus, of whose parents it was said: 'Les parents ne présentent pas d'affection similaire: cependant la mère prétend, que pendant sa grossesse elle avait grand soif et urinait beaucoup'. Wolff (1903) describes a man with diabetes insipidus, who had two brothers similarly afflicted. 'Der Patient macht die interessante Angabe, dass die Mutter harnruhrkrank war, während sie mit den jüngsten drei Söhnen schwanger war: auch jetzt soll sie noch an der Krankheit leiden und täglich c:a 4 Liter Urin ausscheiden'.

The two latter passages from the literature are the only ones the author has found which agree fully in their treatment of the phenomenon which, in the present work, is described in numerous conductors of diabetes insipidus.

In connection with the pathological increases of urine during pregnancy, different authors (Klaften 1927, Momigliano 1929, Novak 1917, Schellenberg 1930, and others) have pointed out

that, even physiologically, there is often a greater quantity of urine, with lowered specific gravity, towards the end of this time. This information is universally found in the obstetric text books (von Winckel 1903, Döderlein 1915, Shears 1924, Halban and Seitz 1925, and others). The investigations underlying this view seem to be fairly old, but may nevertheless be accorded weight, since the methods for measuring urine quantities are not new. According to references in Halban and Seitz, Zangemeister has found the average daily output of urine in women near their delivery to be 1,461 cc, as against 1,200 cc in non-pregnant women. Henschel (1889) measured the daily output in 39 women near the end of pregnancy, and obtained an average of 1,818 cc, as against an average of 1,448 cc for 100 puerperants.

Bar (1907) quotes a series of authors who investigated the amount of urine in pregnant women, and found a rise during the last 2 months of pregnancy; this rise was more marked among multiparae (Heinrichssen, quoted from Bar 1907, Zacharjewsky 1894, Keller 1901).

The increase in the quantity of urine has been found to run parallel with a fall in the specific gravity (von Winckel 1865, cited from Bar, 1907). Zacharjewsky (1894) found the specific gravity to be lower in multiparae (average: 1.012) than in primiparae (average: 1.020). Bar and Daunay (1905) measured the amount of urine passed by two bitches both during successive pregnancies and in the intervals in between, the animals being kept on a constant diet. They found some increase in quantity during the pregnancies.

Bar sums up his point of view as follows: Polyuria is not a constant phenomenon at the end of pregnancy, but it occurs among a number of primiparae and is usual in multiparae. In certain women it may reach high values: 2,700 cc.

It seems natural to seek a common explanation for this physiological polyuria in pregnancy and the pathological forms of pregnancy polyuria, which appear to be caricatures of the physiological phenomenon. Several of the younger authors have linked it up with the changes, first studied by

Erdheim and Stumme (1909), that pregnancy sets up in the anterior lobe of the hypophysis.

According to the investigations of Erdheim and Stumme and, later on, of several others, the female hypophysis undergoes a regular and considerable increase in weight during pregnancy, due to the increase in the size of the anterior lobe. This lobe is also changed histologically, due to the appearance of the so-called pregnancy cells. There is no need here to take sides in the argument as to their nature. The size of the organ increases with the number of pregnancies, the enlargement being therefore plainer in multiparae than in primiparae. The pregnancy cells appear earlier on and in greater numbers with repeated pregnancy. Both the increase in size and the histological changes become clear from about the middle of pregnancy, and the changes reach their maximum from the 7th month up to partus. After partus the weight of the organ diminishes, and even after as little as a week plain histological involution changes are to be seen. The regression is not complete, however, in that the weight does not return to its initial value, at any rate not for several years. A certain permanent increase in weight therefore remains after each pregnancy.

Příbrský (1934) saw a purely mechanical connection between the pregnancy changes of the anterior pituitary lobe and diabetes insipidus gravidarum; in his view, the enlarged anterior lobe pressed on the posterior lobe, thereby deranging the antidiuresis. On the other hand, Anselmino and Hoffman (1930), Wermer (1938), Mondt (1941) and Vignocchi (1941) refer to the observations of the diuretic anterior lobe principle, and imagine an increased secretion of this during pregnancy.

Hereditary diabetes insipidus.

Delimitation.

The only form of the disease taken up for treatment is the one where diabetes insipidus appeared as the main or the sole symptom. The syndrome called Lawrence—Moon—Bardet—Biedl is admittedly hereditary, and diabetes insipidus may here

appear as a constituent symptom. It is outside our province to discuss whether diabetes insipidus in this disease is due to a gene with isolated effect or to genes with some other effect also. As, in any case, there can be no question of any genotypical identity between this disease and 'pure' diabetes insipidus, it has not been included in the survey of the literature. As has already been pointed out by Warkany and Mitchell (1939), it is not always possible to draw hard and fast lines when studying the literature. A number of reports in the older texts involve a factor of uncertainty, as the cases are scantily described and other symptoms than diabetes insipidus may have been disregarded. This is of no very great importance, as the large materials and the more recent works allow of no doubt as to the delimination used here.

Genetic viewpoints.

Earlier on, it was only when several cases of a disorder occurred among closely related persons that heredity was brought into question. Authors still love to publish such cases. Now, if it is true that the disease can be inherited in different ways, it is obvious that the dominantly inherited forms have far more chance of being recognized as hereditary. Families with many cases of disease arouse interest more readily than sporadic cases, and are more extensively published. It must also be taken into account that cases may happen to accumulate where there is recessive heredity, so that a picture reminiscent of dominance arises. One must be on one's guard against these misleading eventualities, above all in the older literature, and not be tempted to the statement that a recessively inherited form does not exist because a dominant form is known.

As regards diabetes insipidus, the fact is that practically all the earlier literature on its hereditary forms is in the shape of reports on pedigrees. The first of these reports appeared almost exactly 100 years ago, from Lacombe (1841). Compilations of earlier reports have been made by Bulloch (1909) and Hanhart (1940), who in so doing also discussed different ways in which diabetes insipidus might be inherited. de Lange (1935) gives a critical survey of the older literature, and

Warkany and Mitchell (1939) have a short discussion on the heredity of the disorder.

To give a better survey, I have collected the pedigrees to which I have had access in table 2, where some genetically important features — to be discussed later — are noted. One column gives the presence or absence in the pedigree of the passage of the disorder from father to son. When such passage exists, the gene cannot possibly lie in the sex chromosome. The last column shows whether or not a female generation has been skipped, a customary, though by no means conclusive phenomenon in sex-linked heredity. The pedigrees will be discussed not in chronological order, but in order of their different genetic types.

The pedigree compiled by Weil, father and son, and complemented by Camerer, has been published in stages: 1884 — 1908 — 1935. It is classical within diabetes insipidus literature, and derives its importance from its size and the circumstance that nearly all its members have been traced and investigated — though not necessarily in hospital. The reports of the presence or absence of the disease in the individual cases are therefore fairly convincing. The affected subjects comprise 23 men and 14 women, spread over 6 generations. With one exception, the passage from one generation to the next is without a skip. There are numerous cases of direct inheritance from father to son. According to Camerer, the ideal ratio between the number of affected and healthy sibs (such as 1:1), which is found with a clear-cut dominant gene, is here realized. It is due to this pedigree that the literature has adopted the fairly dogmatic view that diabetes insipidus is exclusively inherited on the pattern of clear-cut dominance.

Finally, an irregularity in the Weil pedigree should be pointed out. In Generation IV there is a healthy woman who is the daughter of an affected man, and who has an affected son. By itself, this section of the pedigree would look like a case of recessively sex-linked gene. But we know that this is not so. Three possibilities then offer themselves. The disease of the grandchild may be due to environmental injury, and therefore non-hereditary. Or, the boy may not be the son of the

Table 2.

Cases of familial diabetes insipidus from the literature.

Authors	Publishing year	Number of affected subjects	Males	Females	Generations	Father-son-passage	Skipped females
Lacombe	1841	8	5	3	2	+	—
Deebrey	1859	5	2	3	2	—	—
Wachsmuth	1863	2	2	0	1	—	—
Gee	1877	11	9	2	4	—	+
Pain	1879	7	5	2	3	+	—
Orsi	1881	6	5	1	2	—	—
Weil, Adolf — see Camerer	1884						
Clay	1889	3	2	1	1	—	—
McIlraith	1892	10	7	3	3	—	(+)
Lauritzen — see Ellermann	1893						
Marinesco	1895	2	2	0	1	—	—
Wolff	1903	4	3	1	2	—	—
Knöpfelmacher	1905	5	3	2	4	+	—
Weil, Alfred — see Camerer	1908						
Ehrmann	1911	3	3	0	1	—	—
Jansen & Broekman	1921	14	4	10	4	+	—
Mensi	1922	5	1	4	3	—	—
Martinez & Navarro	1922	8	7	1	3	+	—
Gänsslen & Fritz	1924	19	10	9	5	+	—
Chase	1927	22	?	?	5	+	?
Peterman	1929	3	3	0	3	+	—
Chester & Spiegel	1933	7	3	4	4	—	—
Komai	1934	5	5	0	2	—	+
de Lange	1935	8	2	6	4	—	+
Camerer	1935	37	23	14	6	+	+
Levit & Pessikova a)	1936	2	0	2	2	—	—
b)	„	3	3	0	3	+	—
c)	„	2	2	0	1	—	—
Bryan & Metzger	1938	2	0	2	2	—	—
Ellermann	1939	26	15	11	5	+	
Steiner a)	1939	2	1	1	2	—	—
b)	„	3	2	1	3	+	—
Scherrer	1940	9	3	6	5	+	—
Gaupp	1941	7	3	4	3	—	—
Mondt	1941	4	1	3	3	—	—
Thaddea & Kleinschmidt	1942	11	7	4	5	+	—

official father, but that of some other man with hereditary diabetes insipidus. Neither of these possibilities are quite out of the question here, on the following grounds: 1) the grandson is the only one of 7 sibs who contracted the disease. 2) the skip is the only one there is in this large pedigree. It would, however, not be flying in the face of fact to accept the third possibility, namely that there really is a skipped gene-bearing female in the otherwise regular pedigree; such a situation is not unknown. It is customary to speak of irregular dominance or, to use a more common term nowadays, of varying penetrance; this says nothing as to why the disease is not manifested by the gene-bearer in the skipped generation. The term 'penetrance' will be discussed further in connection with an irregularity of this kind in the author's material.

Another large pedigree — from Denmark — with impeccable simple dominance was begun in 1893 by Lauritzen, and continued in 1939 by Ellermann. It shows no irregularities. Another such case with numerous affected members was reported in 1924 by Gänsslen and Fritz. By means of genealogical investigation, two groups of affected subjects, previously unaware of their kinship, were traced back to a pair of common ancestors who married in 1680; this means the gene has been followed through 8 generations, though reliable data exist only from the 5 youngest.

Practically all the more recent works on hereditary diabetes insipidus have assumed that the gene is inherited by simple dominance; they have further stated that the male sex is more liable to the disease than the female (Weil Jr. 1908, Jansen and Brockman 1921, Chester and Spiegel 1933, de Lange 1935, Warkany and Mitchell 1939, Scherrer 1940, Hanhart 1940, Marx 1941). Hanhart tabulates 25 pedigrees, thus getting 169 affected subjects, of which 108 (i.e. 63.9 %) are men. This is a significant difference from the 50 ± 3.85 to be expected in a random distribution of the sexes. If the author's material in table 2 is added, we get 243 affected subjects, of which 143, or 58.8 %, are men. Here the standard error is 3.2 %; the deviation from the expected 50 % is not quite 3 times this, but well over twice, and therefore probably significant. The ob-

servation that the male sex is more often affected has been used as an argument by Lickint (1934) in a work where he answers in the affirmative the question 'Ist der Diabetes insipidus eine genitohypophysäre Erkrankung?'.

Günther (1942) suggests that the dominance of the male sex is actually to be explained by the presence of a sex-linked hereditary form of the disease. If this is the case, and the older material is consequently not genetically homogeneous, it is not right to calculate the sex distribution without preliminary selection. The small pedigrees where only one generation has been observed cannot be referred to any one course of heredity, and this is true of some of the larger pedigrees, also. To get as homogeneous material as possible, the author has tabulated below those 13 pedigrees within which passage from father to son is known (Chase's pedigree had to be left out, because the sex of the affected members was not always given). A selection of this kind removes all x-linked genes.

Table 3.

Number of affected males and females in the pedigrees showing father-son-passage.

Authors	Males	Females
Lacombe	5	3
Pain	5	2
Knöpfelmacher	3	2
Jansen & Broekman	4	10
Martinez & Navarro	7	1
Gänsslen & Fritz	10	9
Peterman	3	0
Weil, Weil & Camerer	23	14
Levit & Pessikova b)	3	0
Lauritzen & Ellermann	15	11
Scherrer	2	1
Steiner b)	3	6
Thaddea & Kleinschmidt	7	4
	90	63

It is clear, however, that the above selection is one-sided and must favour the figure for men, since the criterion with inheritance from father to son presupposes at least two male

members of the pedigree. The selection error must be corrected in each pedigree by subtracting the selected cases, i.e. 2 men. The figure 90 will thus be lowered by $2 \times 13 = 26$. This then gives the sex ratio of 64:63, which comes as close to the ratio of 1:1 as can reasonably be demanded. All this seems to me to show that there is no justification for talking about a predominance of the male sex in a material of hereditary diabetes insipidus, if one has not convinced oneself that the sex-linked genes have been eliminated.

Let us say, then, that a material freed from sex-linked genes has no surplus of affected men, while the total material has a statistically significant surplus of this kind; it would then seem most natural to assume that there is, in point of fact, also a form of diabetes insipidus which is inherited in a sex-linked manner. Even earlier publications of material contain pedigrees lending themselves to such an assumption, and these will now be discussed.

The idea that diabetes insipidus can be inherited in the same way as haemophilia is sometimes found in the literature. The first instance is in Liebmann (1888), who rejects the idea.

Fig. 1 shows the pedigree communicated by McIlraith (1892). It appears that the 7 affected male members are denoted as suffering from extreme thirst, or quite simply as affected. The 3 female members are said to be slightly affected. It is these slightly affected women who conduct the gene. McIlraith writes that 'it seems to be a heredity occurring chiefly in the males on the female side of the house' — the idea of sex-linked heredity could hardly be expressed more clearly. If this heredity is accepted, it is easy to find a simple explanation for the fact that the women are more slightly affected than the men: they are heterozygotes and the gene has an intermediary effect. The author's material contains sections of pedigrees which tally exactly with that of McIlraith: the heterozygotes are slightly affected.

With McIlraith in mind, a number of later authors discuss the possibility of sex-linked heredity (Weil Jr. 1908, Jansen and Broekman 1921, Weitz 1936, Hanhart 1940). They all repudiate the idea. Hanhart agrees with Weitz that the as-

sumption of dominant heredity even in McIlraith's case is the most plausible. Compared with the large pedigrees — above all that of Weil — where an autosomal gene was unquestionable, the hitherto published small pedigrees with possibly sex-linked genes have borne less conviction. Warkany and Mitchell (1939) point out that the simple dominant hereditary mechanism has been proved, but that it cannot cover all cases.

Nevertheless, a pedigree communicated by Komai (1934),

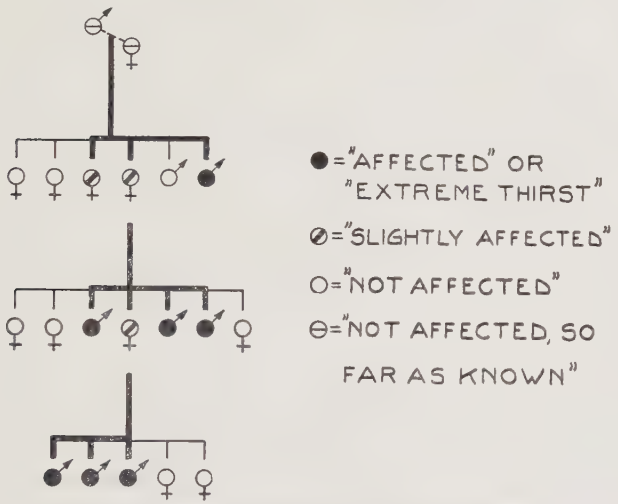


Fig. 1. Pedigree published by McIlraith 1892.

and reproduced according to Hanhart (1940) in fig. 2, is considered by this latter investigator to argue strongly for a sex-linked gene. It is true that the picture has the caption 'Apparently recessively sex-linked pedigree', but the reservation can hardly imply more than that the material is thought so small that the distribution arose at random. The pedigree would seem to answer all requirements: the affected subjects are all men, sons of healthy mothers. There is no passage from father to son. In his essay of 1942, Günther mentions the pedigrees reported by McIlraith and Komai as probable cases of sex-linked heredity.

The already mentioned pedigrees of Marinesco (1895) and Wolff (1903) may probably also be assumed to belong to the

sex-linked group. The cases concern 2 and 3 affected brothers respectively, whose mothers had symptoms in connection with pregnancy, but not otherwise.

As table 2 shows, still other pedigrees show skipped females with concurrent absence of father-to-son passage. Gee (1877) followed the disease through 4 generations without seeing any passage from male to male. In 3 cases the gene was passed on by healthy mothers, and in 1 case by an affected mother. There

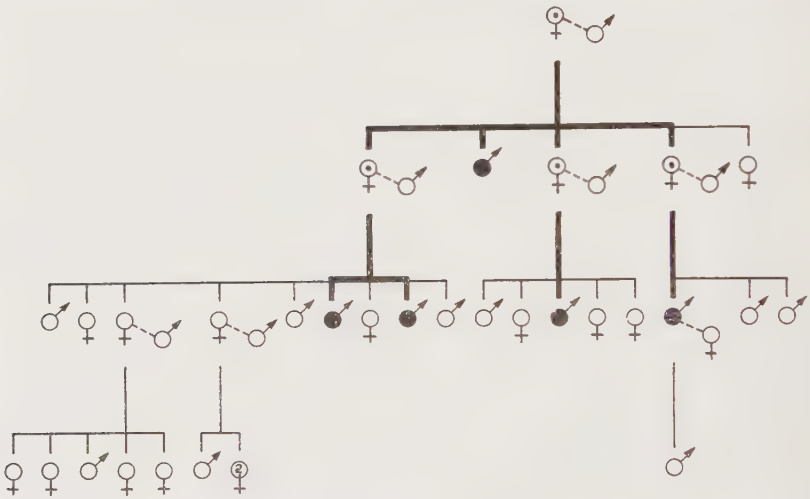


Fig. 2. Pedigree published by Komai 1934, re-drawn from Hanhart.

were 9 affected men to 2 affected women. No mention was made as to whether the affected women were less affected than the men.

de Lange (1935) has similarly followed the disease through 4 generations; in no case was it transmitted via male sufferers. In 1 case the female conductor is denoted healthy; in 3 cases the gene is passed on by affected mothers. There are 6 affected women to 2 affected men. The 2 women examined in more detail had the disease in so mild a form that they agree well with the heterozygotes which the present author will be describing. There is nothing definitely indicating that these cases cannot also be referred to the sex-linked group. On the other hand, it is a common objection that too many affected

women have been recorded. The possibility — already touched on in connection with McIlraith's pedigree — that the female heterozygotes may to a certain extent be phenotypically affected limits the force of this argument, however. The quoted cases may perhaps fall under the heading of sex-linked heredity, or they may on the other hand represent an autosomal gene with irregular penetrance — no more definite pronouncement can be made.

Let us now proceed to those works calculating on other modes of heredity than those discussed hitherto. It has already been said that there is no justification for contesting the occurrence of the recessively sex-linked gene on the score that the simply dominant gene has been proved; an *a priori* rejection of the possibility that there is also an autosomal recessive gene for diabetes insipidus is just as unjustified, though it has already been pointed out that such a gene must be much more difficult to reveal.

The method of starting with a character-bearing proband and seeking for other cases among his or her relations has been used both by Levit and Pessikova (1936) and by Steiner (1939). The difficulty immediately encountered in such a procedure is that it is impossible to draw a hard and fast line between acquired cases and idiopathic or, more correctly, genotypically conditioned ones. Steiner's criterion for an idiopathic case is this: 'Eine äussere Krankheitsursache oder eine organische Veränderung der Hypophyse oder des Zentralnervensystems konnte bei längerer klinischer Beobachtung und Anwendung sämtlicher in Frage kommender Untersuchungsmethoden nicht festgestellt werden'. This eliminates the acquired cases as far as this is possible. It is clear that it should have been expressly pointed out in the works quoted that the group finally obtained is, even so, not homogeneous. A number of the seemingly idiopathic cases may be genetic. Others may be due to an acquired disease, e.g. encephalitis, which provided no other symptoms except diabetes insipidus, and which had not appeared in the anamnesis. Incidentally, Steiner does not consistently apply the limits he himself drew up. His case 6 has a severe cranial trauma in the anamnesis shortly

before the syndrome appeared, but the case has nevertheless been included among the idiopathic, and the cranial trauma designated, merely in passing, as a 'Besonderheit'.

Steiner's family investigations involved tracing the parents. sibs and grandparents of the probands, and also their offspring, as far as possible. In case 1 the mother of the male proband was also found to suffer from diabetes insipidus. As neither of her parents and none of her directly investigated 6 sibs had the disease, it is possible that the gene mutation arose in her. The possibility of a skip cannot be excluded, since the investigation did not go back beyond her parents.

In case 2, both the paternal grandfather and paternal uncle of the proband (a woman) had the disease, while the father did not. This would mean that the rare case of a skipped male was involved. The grandfather and uncle were not investigated direct, being diagnosed only on the evidence of the family, and the symptom-free father was investigated with a single sample of urine, which had the specific gravity of 1.022. The evidence seems convincing, and the pedigree probably did have the appearance given. The passage from father to son shows that the gene is autosomal and dominant, though not regularly penetrant.

Cases 3—6 revealed no character-bearers beyond the probands. As has already been mentioned, Case 6 is, moreover, probably due to trauma.

No case showed relationship between the parents of a proband.

Levit and Pessikova (1936) have submitted a work, partly carried out with the same method as that of Steiner, on the heredity of diabetes insipidus. They investigated the families of 13 probands with 'pure' diabetes insipidus and 3 probands with diabetes insipidus and dwarfism. (The latter group, which never showed relationship between the parents, nor any cases of diabetes beyond the proband, will not be touched on for reasons given at the beginning of this chapter.) 10 of the 13 families had no other affected member than the proband. In the remaining 3, the following members were also affected:

1) the mother of a woman, 2) the father and paternal grandfather of a man, 3) the brother of a man.

In one of the pedigrees, the affected woman had 5 sibs, all unquestionably healthy. In addition, she had 8 unquestionably healthy children (and no affected ones). In another of the pedigrees, reliable reports had been received on 6 sibs of one affected member, and 3 sibs of another; all these sibs were healthy. If a clear-cut dominant gene were in question, it would lead one to expect a ratio between affected and healthy individuals such as 1:1, on adding up the children of the affected members. The distribution between healthy and affected in this pedigree is therefore incompatible with an assumption of this kind.

The conclusion of the cited authors is that diabetes insipidus is due not to a clear-cut dominant gene but to a conditionally dominant gene with poor penetrance. Their observation clearly supports the possibility that even sporadic cases of diabetes insipidus may be genetic. Levit and Pessikova write: 'Our results clearly show the doubtful value (for purposes of genetic interpretation) of selected material gathered from the literature as compared with data that are systematically gathered without recourse to selected familial cases. From a study of Bulloch's data one gets the impression that every case is a familial one. In our material of 16 cases of diabetes insipidus only three were familial'.

This argument is not correct; the authors of the work in question seem here to have forgotten that a number of the probands may conceivably have had diabetes of unknown, non-hereditary genesis. We do not know how many of the 13 non-familial cases can be explained thus. The mere existence of congenital or very early diabetes in sporadic cases provides a certain support for the presence of a recessive gene. The literature does not give any further argument for this mode of heredity.

In no case is consanguinity demonstrated by these authors, either.

In his already quoted work of 1934, Komai has collected 10 pedigrees, most of them small, from 12 Japanese authors.

The present author has not had access to the original, but quotes it here from Hanhart (1940). 3 of the Japanese pedigrees (communicated by Koga 1914, Kurose 1928, and Hitomi and Sato 1928, all quoted from Hanhart) present healthy male gene-bearing individuals — a state of affairs which only Steiner has observed otherwise.

The problems round the heredity of diabetes insipidus exemplify the difficulties encountered when working out characters which are inherited in different ways. The fact that those families where the character-bearers are many are most likely to be published means that a not unduly rare recessive gene may be interpreted as a dominant one, by those working from published pedigrees.

The correct method in uniform heredity is to start with probands and investigate the frequency among the relations. In that case one should take all the character-bearers in a certain area, or in some other way ensure that no selection is involved.

This procedure can no longer be used when a disease is inherited in more than one way. Theoretically, it should then be possible to show that accumulations occur in the family to a greater extent than would answer to the random mechanism in recessive heredity, but less than in dominance. The situation is not so easy when, as in diabetes insipidus, the disease may also be of a non-hereditary nature. The practical working method then becomes both to study pedigrees and to use cases selected at random. A necessary condition is that one has some idea of the frequency of the character in its genetic and acquired forms. One has no good idea of this kind as regards diabetes insipidus.

*

The following works, often quoted in the literature on hereditary diabetes insipidus, have not been included, for the reasons given:

Reith 1866. This work is universally taken to treat hereditary diabetes insipidus, and is still accepted by Hanhart 1940. This is also found to be the case in de Lange, who has otherwise made a

critical selection, but expressly points out that she has not been able to get hold of Reith's original. This must also be true of other authors who have referred to the work, for it only describes a single patient with diabetes insipidus and mentions that a number of relations had glycosuria and albuminuria. From the standpoint of his own time, the author regards the three diseases as varying manifestations of the same gene, and assumes them to be 'interchangeable'.

Lancereaux 1869. This work has in several places been announced as communicating independent cases, but as de Lange, who has herself read the original, has ascertained, it merely describes earlier cases.

Sasse 1893. One case is observed where the daily output sank spontaneously (i.e. without thirst test) to 1,300 cc, with a specific gravity of 1.018. A brother of the patient was observed in an ambulant call, when a single sample of his urine had the specific gravity of 1.020. The other members of the pedigree were not investigated. Recessively sex-linked heredity would seem to be most likely, but no reliable indications of diabetes insipidus are submitted, and the pedigree has consequently not been included. The pedigree is accepted by de Lange, but questioned by Weil Jr.

Roger and Alliez 1936. The work describes 2 pairs of sibs with diabetes insipidus; the first pair, who have many dysplastic features and who recovered spontaneously from their diabetes insipidus, are excluded in view of the general limiting of the present thesis. The second pair consisted of two sisters, both syphilitic and both first contracting diabetes insipidus at the age of 40 years. Despite the homochronism, there is too strong a suspicion that the diabetes insipidus should be attributed to their probably congenital syphilis.

Clinical viewpoints.

With the limits used in this thesis, there are few exceptions to the rule that hereditary diabetes insipidus is, on the whole, a lifetime condition. The symptoms may be seen to disappear immediately before death. The data as to when the symptoms appear vary somewhat, though in point of fact very little — indeed, so little that the few more pronounced deviations acquire interest from the viewpoint of genotypical identity. The following table shows the various reports as to the onset of the disease to which I have had access.

Wachsmuth	Always.
Chase	,,
Gaupp	,,
Scherrer	Since birth.
Gee	,, ,,
Lauritzen	From earliest infancy.
Weil Sr.	,, ,, ,, , 4—6 months of age.
Weil Jr.	From a suckling.
Knöpfelmacher	,, earliest infancy, perhaps since birth.
Jansen & Broekman	From earliest infancy.
Mensi	,, ,, ,,
Ellermann	Immediately after birth.
Gänsslen & Fritz	Since earliest infancy.
Marinesco	From early infancy.
McIlraith	,, infancy.
Levit & Pessikova a)	,, an early age.
Bryan & Metzger	Since early in life.
de Lange	From about 1 1/2 years of age.
Chester & Spiegel	Since as far back as she can remember; in 2 cases, 5 years of age.
Martinez & Navarro	From 2 years of age.
Steiner a)	Since early childhood; since the first years at school.
,, b)	Since the 8th year of life; since childhood.
Clay	From 9 years of age (all 3 cases).
Thaddea & Kleinschmidt	,, 10 years of age.
Levit & Pessikova b)	,, about 20 years of age.
,, c)	,, 16 years of age.
Deebrey	,, about 20 years of age.

Plainly, in the vast majority of cases the diabetes insipidus syndrome sets in, or more correctly is *observed*, very early in life. However, when we get to the cases reported as setting in at 8 –9 years of age, we must allow for the possibility that

the individual concerned really falls ill, and this must certainly hold for those cases observed at the age of 20 years. The last-mentioned cases being so few, and experiences of the opposite situation with very early observed thirst being so many, it seems in order to suspect that there is no genotypical identity between those contracting the disease early, and those contracting it late. The large pedigrees with the well-described cases of pure diabetes insipidus show an early onset throughout. As the age for the onset increases, we tend more and more to suspect that an environmental injury is involved, above all in those cases where the pedigree contains only very few affected members.

All authors with any data on the matter are agreed that the symptoms become most intense at puberty or round the age of 20 years. It has also often been observed that there is a decrease in intensity at advanced ages, e.g. after 60 years; some authors say after 50 years (Gee 1877, Weil Sr. 1884, Weil Jr. 1908, Gänsslen and Fritz 1924, de Lange 1935, Ellermann 1939, Scherrer 1940). During the latter decades of life, the daily output of urine may fall to half its maximal figure. On the other hand, no cessation of the symptoms have been seen other than just before death.

In most cases of hereditary diabetes insipidus, the daily output of urine for young adult patients is said to lie in the vicinity of 8—10—12 litres. Marinesco (1895) gives the figure of 28 litres — a unique value among the hereditary cases. The figures vary downwards towards 3—5 litres, but this is only found in the minority of cases.

The specific weight of the urine is most often about 1.001—1.009. During thirst tests the patients not infrequently approach 1.015. If patients of the same age are compared, the variations within the different pedigrees are not as a rule great. de Lange's (1935) family contains, on the whole, only slightly affected members; it illustrates the difficulties encountered in a number of cases of confirming or ruling out the diagnosis by means of thirst tests. de Lange made a clinical examination of 2 girls, aged 6 and 9 years. Both had had very strong thirst and passed large quantities of urine from early childhood (age of about 1 $^1/_2$ years), and they belonged to a family

with numerous cases of diabetes insipidus. When allowed to drink freely, the 6-year-old had a daily output of 800—950 cc urine, with a specific gravity of 1.008. Under the same conditions, the 9-year-old had a daily output of between 1.350 and 3,550 cc, and specific gravities that kept within the limits 1.004—1.006. After a thirst test from 8 a.m. to 3 p.m. the younger reached the specific gravity of 1.023, and the elder that of 1.022. No ordinary water loading test with subsequent thirst test was made, so that a comparison with known normal values becomes difficult. All the same, it is clear that the concentration approached normal values. We are told, moreover, that thirsting caused the children no discomfort. In view of the family anamnesis and the early observed symptoms, the diagnosis of diabetes insipidus seems very applicable. But it is very doubtful whether such a diagnosis would have been made if the case had been an isolated one, and with a short anamnesis. These slight diabetes insipidus cases of de Lange's tally to a high degree with the heterozygote gene-bearers, which will be described later in this thesis.

According to the literature, it is customary for women suffering from the disease to report a marked increase of thirst during pregnancies, sometimes with a doubled daily output of urine. This phenomenon is fully dealt with elsewhere.

An interesting phenomenon, often described but not so frequently observed, is found in the beginning of the elder Weil's work (1884). His proband came to hospital with typhoid fever. As long as he had a temperature, his consumption of water aroused no comment, but when the fever subsided the diabetes insipidus set in again with great intensity. A considerable decrease of the daily output of urine and an increase of its concentration in connection with fever has been observed in other patients, also, by Weil Sr. and Jr. (1908) and Scherrer (1940), and by Haymann and Fanconi (1926) in a patient belonging to Gänsslen's and Fritz's pedigree. On the other hand, Jansen and Broekman (1921), Gänsslen and Fritz (1924) and Ellermann (1939) have not seen any such decrease in the diuresis of their patients when feverish.

The reaction of the symptoms to the hormone of the posterior

pituitary lobe has a special interest. Reports of a rapid and distinct effect from the administration of this hormone are to be found in Martinez and Navarro (1922), Chase (1927), Peterman (1929), Chester and Spiegel (1933), Bryan and Metzger (1938), Ellermann (1939), Scherrer (1940) and Thaddea and Kleinschmidt (1942). de Lange (1935) has tried out the hormone without eliciting any plain effect; however, she registered the effect only in the figures for volume and specific gravity of the 24-hour urine. Moreover, her cases are of a specially mild nature with figures which approach the normal spontaneously. Haymann and Fanconi (1926), who investigated a patient from Gänsslen's and Fritz's pedigree, did not see any effect on the daily output, either.

Unlike the situation in symptomatic diabetes insipidus, individuals affected with the hereditary form are usually healthy in all other respects, normally developed, without dysplasia or obesity, of normal sex type and normal fertility. Defects of intelligence in some of the diabetes insipidus patients are mentioned by McIlraith (1892) and Ehrmann (1911), but do not seem to have been observed otherwise. It is not customary for the nervous system to show any disturbances. X-rays show the sella turcica to be normal (Mensi 1922, Gänsslen and Fritz 1924, Chase 1927, Chester and Spiegel 1933, de Lange 1935, Ellermann 1939, Gaupp 1941). The lumbar puncture finding is normal (Ellermann). The disease is considered to have an extremely favourable prognosis: in the Weil pedigree 3 patients attain as high ages as 83, 87 and 92 years.

The disorder is not as a rule looked upon as a disease by the families or the affected persons, but as a habit or a peculiarity. And indeed, hereditary diabetes insipidus is an anomaly rather than a disease. The disorder is usually discovered by the physician during consultations for something quite different (Weil Sr. 1884, Gänsslen and Fritz 1924, and others).

Patho-anatomy.

As far as the present author has been able to discover, only two works have reported results of investigations bearing on the patho-anatomy of hereditary diabetes insipidus. This state-

ment does not apply to the descriptions of urinary tracts dilatated by the great diuresis and the like. A patient from Gänsslen's and Fritz's pedigree showed a hypoplasia of the nucleus supraopticus and the nucleus paraventricularis with a reduced number of ganglion cells. The hypophysis and pars tuberalis were reported to be normal. (Data agreeing with this is found in Hanhart 1940 and Marx 1941, but it has not been taken from Gänsslen's and Fritz's work of 1924; the source is not given.)

Gaupp (1941) similarly found in one examined case a paucity of cells in the nucleus supraopticus and, less marked, in the nucleus paraventricularis, as also considerable decrease in the volume of the posterior lobe. The net of nerve fibres and the cells of this lobe were sparser than normal, and the number of nerve fibres in the pituitary stalk was also greatly reduced. No changes were demonstrated in the anterior lobe.

CHAPTER 2.

The collection of the material.

The material started from 7 cases of hereditary diabetes insipidus, treated at the Academic hospital in Upsala during the years 1897—1940. They were spread over 3 different pedigrees, and the first step was to extend these as far as possible by information obtained from the nearest relations. The pedigrees have subsequently been further enlarged, and new cases traced by genealogical research based on the books of the parish registrar and, in one single case, with the help of a law report on a paternity case. The genealogical work has been done by a staff of experts at the Genealogical Office in Upsala. The parish registrars have supplied the addresses of distant relations to the known cases, and the following letter was sent to these relations:

An attempt is at present being made at the Academic Hospital to clarify a rare disease, the so-called thirst disease, which manifests itself in a great consumption of water, necessary to keep the affected persons alive. The amount of water drunk will be about 10 litres or more a day, and the sufferers (who apart from this disorder are just like any other person) are usually known in their family and home surroundings as 'water-drinkers'.

The disease is markedly hereditary, and as water-drinkers of this kind have been found among very distant relations of yours, we beg to put the following questions to you and a number of your nearer and more distant relations; an addressed envelope is enclosed for your answers. The information thus obtained will be used solely for scientific purposes.

Do you know of any such water-drinker among your relations? If so what is his (her) name and age?

To your knowledge, has he (she) ever been in hospital?

Thanking you in advance for your trouble and your help,

310 examples of this letter were dispatched, of which 152 received answers. In many cases the answers led to a correspondence with complementary questions. Furthermore, a large number of relations were interviewed in visits by the author to families with affected members.

As it had already been shown at an early date that there was sex-linked heredity in the known parts of 3 of the pedigrees, the author has in the genealogical work presumed their remaining parts to have this heredity also. The fact was that some limitation was necessary on account of time and expense, and the aim of the genealogical investigation was to trace as many cases as possible, not to achieve a complete exposition of the pedigree. As an x-chromosome-linked gene cannot pass through two consecutive male generations, the paternal forebears of a male proband have not been worked out. The descendants of two consecutive male generations have sometimes been omitted for the same reason.

A clear accumulation of the cases belonging to the largest pedigree could be observed in certain parishes of Örebro län in Central Sweden. When visiting these regions, the author also used to ask persons with many contacts in their community whether they knew of cases showing abnormal thirst for water. A few new cases were traced in this way, and a fourth pedigree discovered which, although geographically close to the large Central Sweden pedigree, cannot be proved conclusively to be related to it.

By the kind permission of the Senior Physicians, the records from departments of a number of hospitals besides the Academic hospital have been studied for cases of hereditary diabetes insipidus; these records extended from the time the archives was begun to 1941 or 1942. The following criteria were adopted: All those cases should be accepted where there was a positive heredity anamnesis, together with all cases who contracted the disease before the age of 10 years, no connection with another disease — e.g. cerebral tumour, cranial trauma, etc. — being demonstrable. With these criteria, not a single case (except 2, which the author knew about already) was found in the following hospital departments:

Medical clinics at the Serafimer hospital and Karolinska hospital in Stockholm.

Medical department of Kronprinsessan Lovisas Vårdanstalt in Stockholm

Medical departments of Sahlgrenska hospital, Göteborg

„ „ at the hospitals in Borås, Falun, Lidköping and Umeå.

Finally, the material has been further enlarged by information from colleagues about cases they had come across. In this way a 5th pedigree came into being.

When cases of diabetes insipidus had become known through the family anamnesis, the aim was to get them under clinical observation. As no therapy could be offered, and as, with few exceptions, the disorder did not discommode the affected subjects and was not regarded as a disease, the patients submitted to stay in hospital either in return for payment, or from interest and a desire to oblige. The patients who did not agree to hospital investigation have in some cases been examined more summarily in their homes. Quite a number of the heterozygote women, who were often subjectively free from all symptoms, did not grasp the point of the investigation and could not be examined objectively. In these cases, little was to be got from an investigation in the home.

As regards deceased members of the pedigrees whom the family anamnesis show to have been affected, the author has naturally tried to confirm the diagnosis by following up visits to hospital, if such existed; this relatively seldom had any success, however, in which case the diagnosis had to be based on the evidence of the relations. As it is often difficult, when reading older literature, to decide whether diabetes insipidus really was present in deceased or non-investigated subjects, the author has elected to summarise the evidence received, instead of merely saying 'diabetes insipidus according to the evidence of the relations', or some such formula.

Testimony as to the presence or absence of the disease has been considered fairly trustworthy when it was given by a parent, a child, a sib, a husband, or a wife of the individual in question. A criterion of the reliability of the family reports is

contained in the fact that the data as to the living sufferers have been collected by the same method as that used for the deceased. It is therefore significant that the reports of the relations as to the presence of diabetes insipidus were confirmed on investigation in all but 2 cases. In one of these (A: VI: 7) there has been confusion with polydipsia in an oligophrenic, and in the 2nd case (C: VII: 9) the diagnosis is uncertain. In one single case a son (F: VII: 2) did not know about the otherwise well-documented disease of his father, but this case concerned a witness with obvious defects of intelligence. Otherwise, the reports of the relatives have tallied very well with one another. Cases of diabetes insipidus have often been known in quite distant relations (e.g. grandmother's brother, grandmother's father, etc.). It is, in particular, common for those suffering from the disease to know about each other to a large extent. On the other hand, the author has also met an affected individual who did not know that others in the family had the same disorder (D: VI: 4, the relations of F: VI: 8). That is to say, without the extensive genealogical investigation, this case would have been interpreted as sporadic.

The so-called water-drinkers are not infrequently widely known in their home tract. Needless to say, less attention is attracted by those living alone, whose work does not bring them into contact with many people. On the other hand, the symptoms do not usually escape fellow-workers at a factory, for example.

The author has not even attempted objectively to exclude the disease in the large number of non-affected in the material. In the Weil pedigree all members of the family, both affected and healthy, have been investigated with samples of urine passed in the presence of the doctor. In the author's material, where the cases are so few and far between, an investigation on these lines would comprise thousands of healthy subjects. Moreover, single urine samples provide only relatively uncertain information. And a hospital investigation of thousands of presumably healthy people has naturally been out of the question. It is probable that the letter of enquiry did not reach all the affected subjects, so that the number of cases described

is a minimum figure. In the reproduced parts of the pedigree near investigated cases, there is every likelihood that those individuals whom the family denoted healthy really did not have any symptoms. On the other hand, it may very well be that there are several cases in the large parts of the pedigree not reproduced. I would therefore like to stress that the unfilled symbols in the pedigrees must not be taken as indicating only unquestionably healthy subjects; the same symbols have also been chosen for those individuals about whom all that can be said is that there is no reason to assume they had the disease.

CHAPTER 3.

Methods.

Measuring of urine volumes.

As the amount of urine passed at one time may vary as much as from about 10 cc to about 1,600 cc, measuring vessels of different sizes have been used. The small amounts have been measured to the nearest cc, larger portions to the nearest 5, 10 or 20 cc. Thus, even if the absolute exactitude has varied, the relative exactitude is on the whole uniform. The daily outputs have been measured in 1 litre vessels, graduated in 100 cc.

Determination of the specific gravity.

The author has used an areometer for urine (a so-called urometer) of the current model, graduated with lines for one unit in the 3rd decimal. The urometer was standardized by testing with fluids of a known specific gravity, and the author's figures corrected for the slight false indication that was present. The instrument is graduated for use at 15° C, and the samples of urine were chilled to this temperature before determination, so that no correction for temperature was necessary. The specific gravity was read off twice for each determination. With values of a greater importance, the author asked some impartial colleague or nurse to make an independent reading. The values for specific gravity which were taken from older records or from other hospitals could be compared with one another and with those obtained by the author only if the variation between different current urometers was taken into account. According to single tests made by the author with 10 areometers, it is necessary to allow for errors in both directions of at least 4 units in the 3rd decimal.

Chloride titration.

The chloride titration was done according to Bang and Larsson. Urine with a volume of about 20 cc was shaken with animal charcoal and filtered. 10 cc were pipetted off. To this were added 2 drops of 20 % potassium dichromate solution as indicator, after which titration was made with N/10 silver nitrate solution. The figure of the amount in cc of the solution used must be multiplied by 5.85 to give the result in $^0/_{00}$ NaCl.

CHAPTER 4.

Sex-linked genes. Genetic viewpoints.

The pedigrees.

In the largest of the author's pedigrees, called AG, severe or mediumly severe forms of the disease are found only in the males. The female gene-bearers are either phenotypically healthy or else slightly affected, compared with the males.

The disease has without exception been transferred by wo-

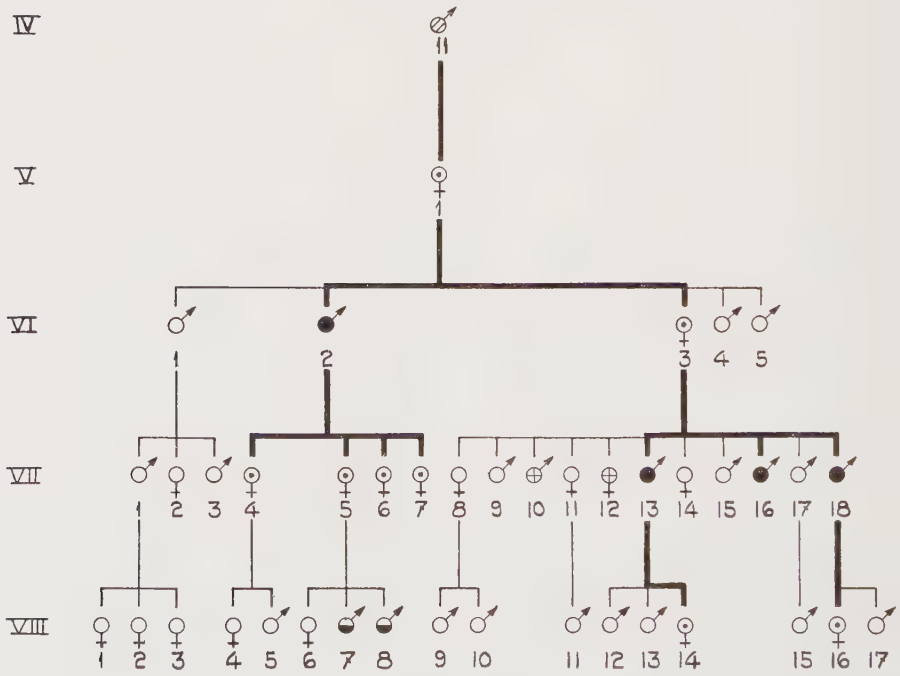


Fig. 3. Family E, a section of the pedigree AG.

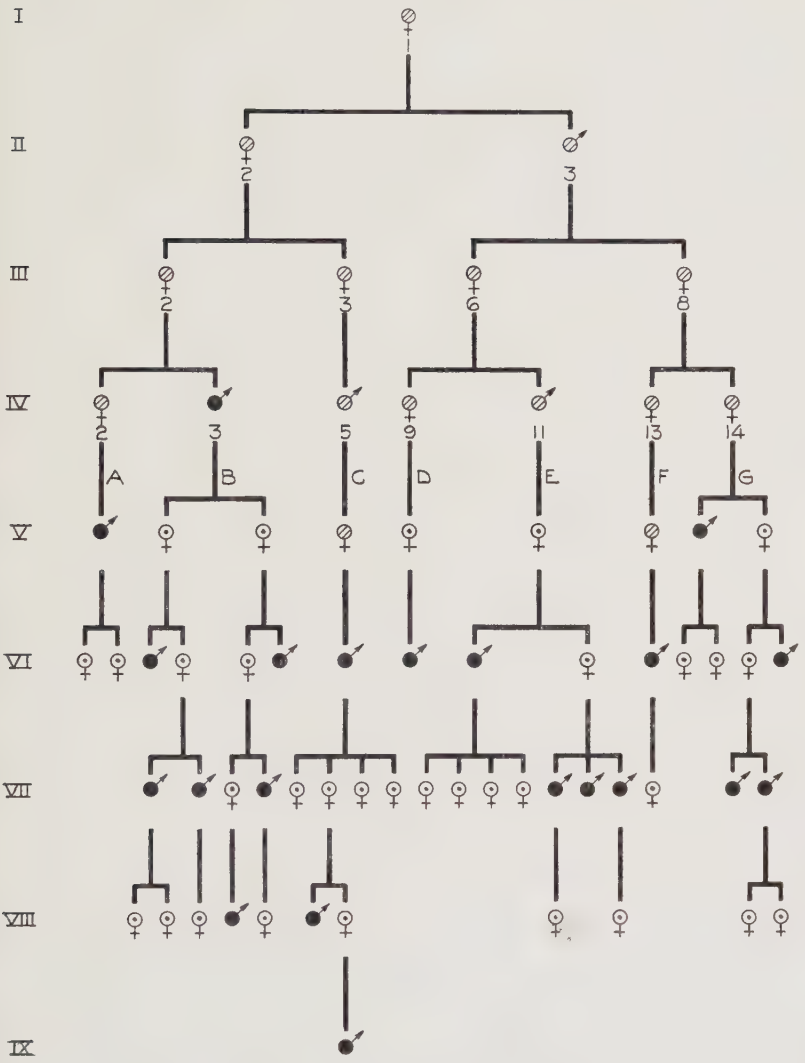


Fig. 4. Summary sketch of the pedigree AG, including only the known gene-carriers.

men. Nowhere has the gene passed from one male to another. The descendants of a phenotypically healthy male have all remained healthy. All this fits in with the assumption of a gene in the sex chromosome.

Genealogical research has shown the 7 families A—G to belong to the same big pedigree, of which the 4 oldest generations, with the first female ancestor born in 1712, are sketched out in fig. 32. As an illustration of the sex-linked heredity, one section of the pedigree (the so-called family E) is shown in fig. 3. The other sections (which have been called families, to distinguish them from the total pedigree) are outlined in the Case Histories. Fig. 4 gives a general outline of the whole

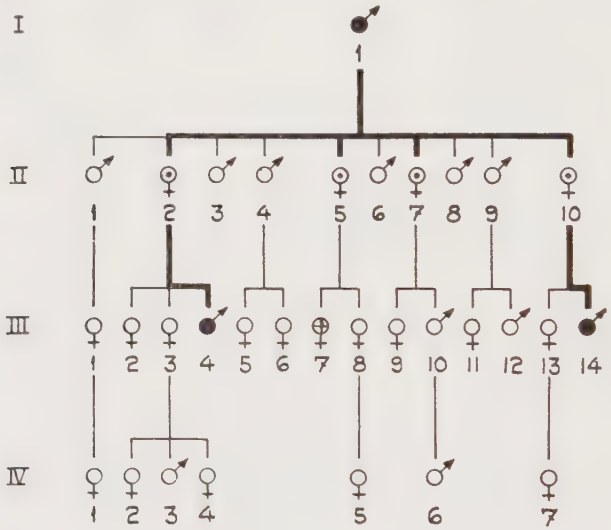


Fig. 5. Pedigree H.

pedigree, in which only the gene-bearers have been included, i.e. those parts which are indicated by the heavy lines in the detail figures. Those parts of the pedigree, too far back for any data of the separate individuals to be obtained, have also been possible to draw in such a way that no 2 male generations followed upon one another. It should be mentioned, however, that alternative possibilities have offered themselves at some points, on account of intermarriage in older generations. The alternatives not given in the figure nevertheless include passages from father to son; it is therefore likely that the gene was passed on in the way depicted. The author hence confines the proof of sex-linked heredity to those parts of the

pedigree which can be surveyed in detail, though the prolongation of the pedigree backwards is also fully compatible with the assumption of a sex-linked gene.

In theory, it is obvious that if one takes a small number of the population and follows their family trees backwards, one will very often arrive at a common ancestor who is more or less arbitrarily chosen from among a very large number of

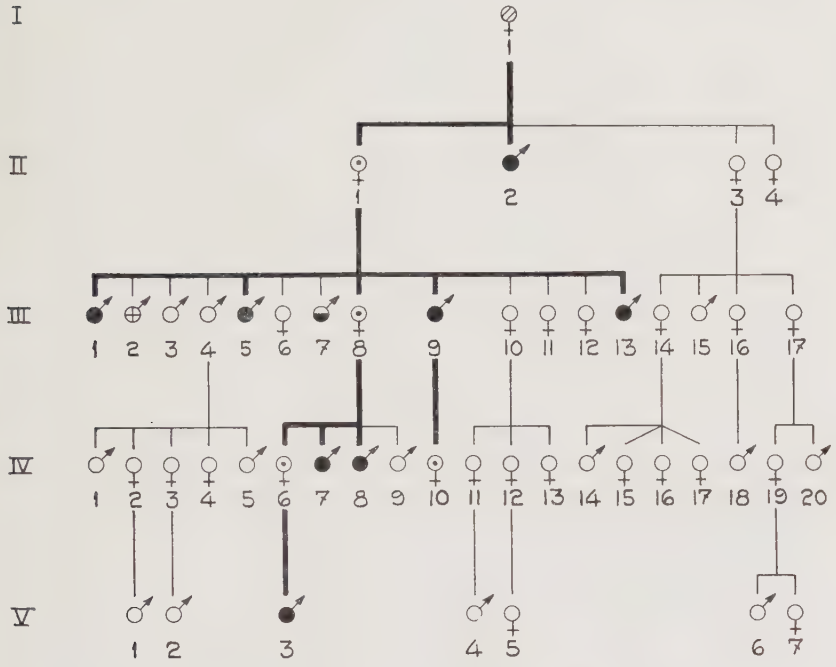
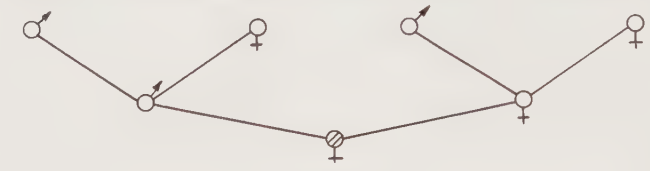


Fig. 6. Pedigree J.

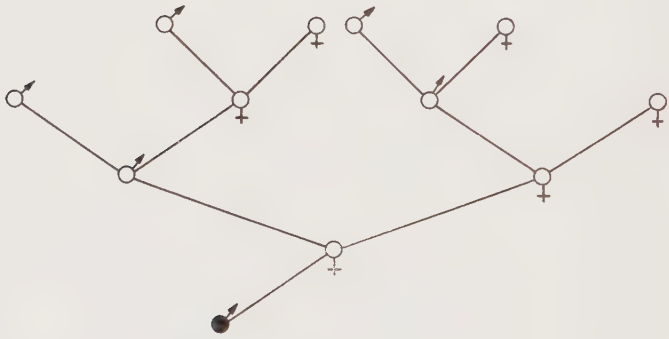
ancestors. However, in questions of a disease which, practically speaking, occurs only in one region and which is extremely rare, there are good reasons for evaluating a common derivation of this kind as a proof of heredity, particularly if it has been necessary to go back only a moderate number of generations. In other words, the demonstrating of a common ancestor is a way of accentuating that the cases of disease occurred within a small area.

Pedigree H, fig. 5, also follows the sex-linked pattern according to the criteria drawn up above. In all probability this family

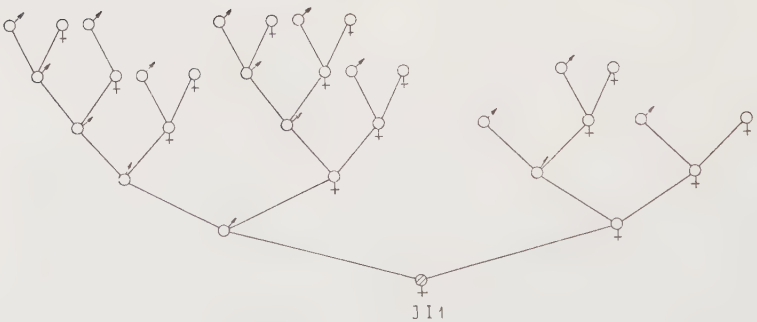
belongs to the same large pedigree as families A—G. The affected man in the oldest generation was born in the parish of Hjulsjö, which adjoins Hällefors, where his mother was



AG:I:1



H:I:1



J I 1

Figs. 7—9 showing to what extent the family trees are genealogically worked out backwards in time from respectively AG: I: 1, H: I: 1, and J: I: 1.

born. Hällefors is the very parish where most of the large pedigree's members were born. The members of family H show the same clinical picture as those in families A—G. The inability to prove a genealogical connection may be due either to

the fact that the investigation has not gone back sufficiently far, or to an extramarital relationship not registered in the parish books. As it seems so highly likely that pedigree H and pedigree AG actually both belong together in a larger scheme, the author will, when dealing with the clinical results, lump together the patients of these pedigrees into what will henceforward be called group AH.

Pedigree J, fig. 6, also presents sex-linked heredity. This mode of heredity is suggested by Generation III alone, with its many sibs: 4 of the 8 brothers contract the disease —none of the 4 sisters do. Now, the geographical position of pedigree H has already indicated that it may be part of the large pedigree AG, and it would seem as though pedigree J might well be added to these two on the same assumption. Even 'Central Sweden' is a pretty narrow geographical direction, and as the disease has been so rare that the form inherited via the sex chromosome has not previously been accepted, the 3 Swedish pedigrees may reasonably be thought to go back to a single mutation. Figs. 7—9 show how far back the family trees of these pedigrees were taken without coinciding. Needless to say, the connection may nevertheless have existed. However, certain clinico-physiological differences can be shown between the patient group AH on the one hand, and the group J on the other, which make it likely that different mutations are involved.

Manifestation frequency.

With a sex-linked gene, the offspring of the woman conductors would theoretically be expected to include affected sons in the ratio of 1:3 in proportion to other sibs, and 1:1 as regards healthy sons. When checking this on the author's material, one has to confine oneself to those heterozygotes all of whose offspring can be surveyed. Siblings dying in infancy or with otherwise uncertain diagnoses are not included in the calculation. The fully documented parts of the pedigrees contain 40 certain heterozygotes. Of these, 18 are childless. The remaining 22 must be divided up in the following way at the calculation. For those women whose heterozygotic character

has been established by the presence of the disease in their respective fathers, the calculation can be made by simple addition of the children, without danger of selection errors. This applies to the 10 conductors in table 4. The remaining conductors are, in their turn, daughters of conductors, and they are determined as heterozygotes by means of some one of their affected sons. The selection must hereby favour the figure

Table 4.

Children of conductors, diagnosed as heterozygotes on diabetes insipidus in their fathers.

Conductors	Number of children	Uncertain	Affected sons	Unaffected sons	Daughters
B: V: 5	6	0	1	1	4
B: V: 7	6	0	1	3	2
C: VII: 4	5	1	1	2	1
E: VII: 4	2	0	0	1	1
E: VII: 5	3	2	0	0	1
G: VI: 13	2	0	0	1	1
H: II: 2	3	0	1	0	2
H: II: 5	2	1	0	0	1
H: II: 7	2	0	0	1	1
H: II: 10	2	0	1	0	1
	33	4	5	9	15

for affected sons. The error must be corrected by subtracting the proband and making the calculation on the remaining sibs. As each of the affected sons may be a proband, the calculation of the sibs must be made for as many times as there are affected sons. The procedure agrees in principle with the one used by Weinberg (1913) in his well-known 'proband methods'. The material thus treated is assembled in table 5: the last 3 columns give the number of affected sons minus 1, the number of healthy sons, and the number of daughters — all 3 items multiplied by the number of affected sons.

If we look first at the figures in table 4, the material is of course small, and the chance of random variations therefore great. Of 14 sons, 5 are affected — that is to say, 35.7 % instead of the 50 % which would, in theory, be expected. When calculating the standard error according to the formula

$$\sqrt{\frac{50 \cdot 50}{14}} = 13.3\ \%$$

it is found that the deviation from the expected result is about as large as the standard error, and may therefore very well be due to chance. Of 29 children, the 5 affected sons comprise 17.2 ± 8.0 % — that is to say, a deviation from the expected 25 % not really greater than the standard error.

Table 5.

Children of conductors, diagnosed as heterozygotes from any one of their affected sons.

Conductors	Number of children	Uncertain	Affected sons (A)	Unaffected sons (U)	Daughters (D)	A(A—1)	A.U	A.D
B: VI: 17	7	0	2	3	2	2	6	4
B: VI: 31	6	2	1	0	3	0	0	3
B: VII: 58	3	0	1	0	2	0	0	2
C: VIII: 8	1	0	1	0	0	0	0	0
D: V: 1	5	0	1	1	3	0	1	3
E: VI: 3	11	2	3	3	3	6	9	9
F: V: 8	1	0	1	0	0	0	0	0
G: V: 8	4	0	1	1	2	0	1	2
G: VI: 31	4	0	2	1	1	2	2	2
J: II: 1	13	2	4	2	5	12	8	20
J: III: 8	4	0	2	1	1	2	2	2
J: IV: 6	1	0	1	0	0	0	0	0
						24	29	47

In table 5 the agreement is as good as can reasonably be demanded, and it is therefore unnecessary to try and calculate the standard error, which would, incidentally, be a complicated matter. The affected sons comprise 45.3 % of all sons and 24.0 % of all sibs. Thus, it should be pointed out that chance has favoured the present author, and that a far greater deviation might still not have exceeded the limits of the random variation.

It has consequently been shown that the manifestation frequency in the author's material agrees with the assumption of a sex-linked gene.

Intermarriage, whereby homozygote women might have been produced, has not occurred in the known parts of the pedigrees.

The older sections of the large pedigree show several cases of consanguinity marriages, but in these cases at least one of the two parties always belonged to parts of the pedigree presumably free from the diabetes insipidus gene. One such indifferent intermarriage has also occurred in family G, as is shown by fig. 39.

CHAPTER 5.

Sex-linked genes. Clinical viewpoints. Affected males.

The material.

The author's material of affected males from pedigrees showing sex-linked inheritance is shown in table 6. Of the 14 classified as investigated by the author in hospital, 2 cases were observed only during ambulant calls, on which, however, it was possible to carry out thirst tests under control, both with and without pituitrin.

Table 6.

Afflicted males from pedigrees showing sex-linked inheritance, divided according to the reliability of the results.

Group	Number of cases	At the beginning of the investigation				
		dead		living		
		Diagnosed from evidence received	Clinically verified	By author investigated		Elsewhere clinically investigated
				in hospital	in their homes	
A H	24	9	1	12	2	—
J	8	3	2	2	—	1
Total	32	12	3	14	2	1

Time of the first appearance of the disease.

Without any exceptions the male patients examined by the author had had their symptoms for as long as they could remember — they knew no other state. The reports of their

relations would also as a rule testify that the affected subjects had 'always' suffered from abnormal thirst. In point of fact it is precisely this latter testimony which is of importance when distinguishing in the evidence between diabetes insipidus and other diseases with great consumption of water which may be elicited from the family anamnesis, above all diabetes mellitus. In these other conditions, the time of a later onset is generally known. Needless to say, the mothers have the greatest possibilities of making observations and discovering the thirst disease at an early date. The author has met 8 conductor mothers, and corresponded with a 9th. The following table outlines the evidence of these mothers, giving as far as possible in their own words their answers to the question: When did you first notice the disorder in your son?

Mother	Affected son's year of birth	Interrogated year	Answer
B: VI: 17	1893	1940 (letter)	At the age of 3 years
„	1895	1940 „	„ „ „ „ „ „
B: VI: 31	1898	1944	When he was an infant
B: VII: 58 ...	1924	1943	At the age of about 2 weeks
C: VII: 4	1912	1943	From the very beginning
C: VIII: 8 ...	1940	1943	„ „ beginning
G: VI: 31	1899	1943	„ „ very beginning
„	1905	1943	„ „ „ „
H: II: 2	1922	1943	When he was a year old
J: IV: 8	1914	1941	The boy died at the age of 17 months. Had previously received medical attention for his thirst.
„	1921	1930 (records)	Since he was quite small
J: IV: 6	1941	1943	From the beginning

In the records of J: III: 5 written in 1897, J: III: 9 (who was then 9 years old) was reported to have drunk 'since birth'; J: III: 13, who was 1 year old when the record was written, was already registered as a water-drinker.

In the light of these data, it seems reasonable to assume that the disease in these pedigrees is literally congenital, as in most

of the cases of hereditary diabetes insipidus in the literature. A failure to notice the symptoms before some time has elapsed is natural in view of the fact that the diet of infants always contains a great deal of water, and their urine is always abundant and diluted compared with that of adults. A 14-day-old child requires 500 gm of water daily, a 6-month-old needs 1000 gm, and an adult 2000 gm; this calculated per kg body-weight, is 167 gm, 143 gm and 32 gm respectively. It is true that the extrarenal water losses of the infant are far greater than those of the adult; nevertheless, the urine of the healthy infant has a specific gravity of 1.002—1.004. (The figures are taken from Bessau, 1938). It should therefore be possible to talk of a physiological diabetes insipidus in the infant. In spite of this, observant mothers can notice the abnormal need of water even as early as about the 2nd week of life (though, of course, this report from a single source may be a loose assumption backed up by chance). It seems definite that the thirst is most often observed during the first year of life. What the mothers usually notice is that these children suck more eagerly than is normal at wash-cloths, drink their bath water etc. They cry at night, and can be quietened only with water. When the mothers know about the family disease, they can naturally make a diagnosis more easily than in those branches of the pedigree where any knowledge of the disorder has been lost.

The intensity of the disease and its variations.

As objective expressions of the intensity of the disease, we can select

1) the amount of liquid imbibed
2) the daily output of urine
3) the specific gravity of the urine.

Of these data, 1) is difficult to procure, and reveals no more than the daily output of urine. The author has therefore not used this method of investigation at all. The two other methods also involve very great factors of uncertainty, as the author is well aware.

Daily output of urine. Anyone who has tried knows how

difficult it is to collect the complete daily output of urine even from a patient in hospital. The difficulties are somewhat less if the patient comes to hospital for another disease, and is generally run-down and bed-ridden. But even in these relatively favourable technical circumstances, one must allow for the loss of a certain amount of urine during defaecation, or as the result of various mishaps. If the patient is generally healthy and out of bed, the difficulties of controlling the collection of urine are further enhanced.

The daily output of patients with diabetes insipidus may vary quite considerably from day to day. Just as for anyone else, it may be influenced because the patient has happened to have more liquid in his diet on one day than the next. Variations may also be caused by varying salt content in the diet (Tallqvist 1903, Finkelnburg 1907, Forschbach & Weber 1911, and others). As these patients have a large bladder capacity, passing 1—3 litres of urine at one time, considerable differences may arise between 2 neighbouring days by a chance shift of an evacuation from one observation day to the other. This error loses in force if the quantity is measured on several consecutive days. It is obvious that the urine must be measured over a fair number of days if a good idea of the average quantity is to be obtained. Now, in the author's material such figures covering more than a few days are available only in those cases where the patients had been some time in hospital with complicating diseases. Those coming by request to be investigated could not be observed for more than one or a few days. Moreover, during these few days the quantity of urine was influenced by thirst tests and antidiuretic hormone. Complete quantities of urine were not obtained from all days of observation. On the other hand, the author has taken pains to ensure that no other urine quantities were entered as complete except those where a reliable check had been made that all urine had been collected. When, then, the mean of these few (in one case the only) daily outputs are recorded in table 7, it is in the knowledge that they give only approximate values of the level of diuresis.

The figures for daily outputs have been taken from the

records as follows: Those amounts already denoted incomplete have been omitted. At the Academic hospital, it is customary for the nurses to note the quantity of urine on the temperature chart, and a plus sign is added when the amount measured is not complete. Naturally, the figures without a plus sign cannot be relied upon always to represent the total daily output, but an exclusion of the definitely incomplete figures should nevertheless bring one closer to the correct ones. In two cases the quantities of urine from the last week of life have also been omitted, since they differed greatly from the previous level, and since this pre-agonal fall of the diuresis should not be allowed to influence the discussion of other variations.

In one column in table 7, the highest measured daily output is noted. This is, naturally, a fairly arbitrary figure. It nevertheless has the advantage of representing with more probability than the other figures a complete quantity of urine. On the other hand, the lowest amount of urine measured has not been included in the table, since it is highly likely that a single low figure represents an incomplete daily output, though this does not appear from the hospital records.

The specific gravities were chosen in the following way. The highest and the lowest figure were selected from older journals. In 2 cases complicated by slight diabetes mellitus, the figures were taken only for days when there was no sugar in the urine (this was generally the rule in both cases). The figures have not been corrected for areometer errors, and only with relatively great uncertainty are they comparable with one another and with other figures for specific gravity. These figures from older records are placed in brackets. The figures without brackets have been taken from the author's own investigations, and have been corrected for areometer errors. The lowest and the highest figure was selected from that thirst test which was made without pituitrin. This gives a certain uniformity: the tests were always made at the same time, and after the same instructions to the patients. A number of sources of error are inevitable: the time at which the patient drank during the night previous to the test may vary. A conscientious and interested patient continues to thirst longer

than one who is less interested. The patient's own reports as to the discomfort due to thirst have determined the length of the test, and thus, to a certain extent, the highest figure.

When, as sometimes happened, patients were observed more than once after some years' interval, the figures have been chosen for every such occasion in the way given above.

In accordance with the above principles, selected figures for the affected males from sex-linked pedigrees are collected in table 7.

Variations due to age.

In comformity with what can be read in several places in the literature, a number of the AH patients who lived to be relatively old have reported that the symptoms became considerably less intense after the age of about 40 years. Several cases of decreasing thirst with advancing years have also been submitted by the relatives of affected men now dead.

This phenomenon can be studied in the author's material from an objective view-point, also. The patient B:VI: 34 has been in hospital for relatively long periods at the ages of 42, 54 and 60 years, each time showing a smaller average daily output than the time before; see table 7. The differences between the mean for each 3 occasions are statistically significant. The same tendency can also be read in the figures for the highest daily output measured, and for the specific gravity. The patient G: VI: 34 was under observation in hospital on 2 occasions, at the age of 22 and 56 years respectively. The same tendency appears here, though he was only under observation for 5 days during the latter period.

In Pedigree J, no decrease was registered subjectively by the one rather older patient, 53-year-old J: III: 9, whom the author was able to question on the matter. This patient was under observation for 29 days at the age of 47 years, and for 18 days at the age of 53 years. There is no statistically significant difference between the average daily outputs, but there is a probable one. A source of error here, however, is that he also has diabetes mellitus, which was better regulated on the second occasion. Urine from 46 days was obtained

Table 7.

Clinical data regarding diuretic intensity of affected males from groups AH and J.

Patients	Age in years	Observation days	Average daily output in cc	Maximal daily output in cc	Lowest specific gravity	Highest specific gravity
B: VI: 34	42	28	7,690	12,380	(1.001)	(1.008)
„	54	22	4,090	5,750	(1.005)	(1.012)
„	60	14	2,660	3,450	(1.009)	(1.013)
B: VII: 25	46	19	4,370	6,100	(1.001)	(1.014)
„	50	8	4,100	4,850	1.004	1.011
B: VII: 26	48	2	8,440	9,870	1.003	1.015
B: VII: 61	45	2	6,630	6,750	1.003	1.008
B: VIII: 36	19	3	8,920	10,800	1.002	1.010
C: VIII: 7	31	2	3,820	4,120	1.003	1.004
C: IX: 2	3 1/2	2	1,460	1,710	1.002	1.010
E: VII: 13	52				1.001	1.007
E: VII: 16	47				1.003	1.009
G: VI: 34	22	35	5,640	8,850	(1.003)	(1.005)
„	56	5	3,680	5,000	1.008	1.017
G: VII: 94	37	6	4,530	5,900	1.005	1.013
H: III: 4	20	8	8,300	9,500	1.001	1.007
H: III: 14	16	1	3,600		1.003	1.012
J: III: 1	63	46	7,870	10,600	(1.003)	(1.011)
J: III: 5	18	41	7,490	11,000	(1.002)	(1.003)
„	26	5	8,990	10,000	(1.004)	
J: III: 9	47	29	9,780	15,300	(1.005)	(1.008)
„	53	18	8,590	12,000	1.002	1.004
J: IV: 8	9	12	4,790	7,000	(1.006)	(1.014)
„	23	2	12,720 [1]	13,110 [1]	1.002	1.003
J: V: 3	2 1/2			1,220	(1.005)	(1.007)

[1] In this one case, the daily outputs of urine were measured in the home and without control. The measurements were made during 2 different Sundays, after the patient had been provided with a measuring cylinder and instructed to note down the size of each amount passed. Despite the lack of control, there is no reason to suspect the figure of great error, since the result tallies well with the volume of the amounts obtained during a thirst test made under control. As so few patients within the J group could be investigated, it is of value to be able to include these figures, also.

The two figures between the columns denote single determinations, and consequently there is no average for them.

from the 63-year-old patient J: III: 1. There is no figure for comparison here, but he has, at this relatively high age, the large average output of 7,870 cc of urine. Thus, we can say that Pedigree J has not revealed either subjective or objective signs of a regression tendency as the patient grew older, but no conclusions can be drawn from this statement, on account of the small number of subjects investigated.

Individual variations not due to age.

1. *Within the same pedigree.*

The fact that the gene shows certain variations in its mode of expression in the pedigrees appears most clearly, perhaps, from anamnestic data. Thus, of the 3 brothers E: VII: 13, 16 and 18, the oldest has always had the severest symptoms, and the middle brother the mildest. No. 13 drinks and urinates several times a night, while No. 16 usually sleeps the whole time. The brothers have grown up in the same environment, live very near to each other as adults, and have the same kind of work. At the investigation, the oldest had considerably larger outputs of urine for the half-hour, and a lower specific gravity both at the beginning of the thirst test and at the end. The difference in age is not great, but if it *had* had any influence, it should have produced a difference in the opposite direction.

The cousins H: III: 4 and H: III: 14 have grown up together and live in the same home. At the time of the investigation they were 20 and 16 years old respectively, and they both showed the somatic signs of completed puberty. Here, the disease had always been considered to be clearly more intense in the elder cousin. On investigation he had an average daily output of 8,300 cc. Unfortunately, only one single daily output has been obtained from the younger: however, this figure, 3,600 cc, is appreciably less than the lowest figure for the other cousin, which is 6,800 cc. In thirst tests so performed as to enable comparisons, the elder cousin's specific gravity varied between 1.001 and 1.007, and the younger's between 1.003 and 1.012. There is thus a certain objective support for a difference between the intensity of their complaint.

There is also a clear difference in intensity between the

brothers B: VII: 25 and B: VII: 26, investigated at more or less the same age; see table 7. These brothers, who have lived apart for many years, could not remember having shown any difference during childhood. It is conceivable that the difference may be linked up with the fact that the elder brother was suffering severely from bronchial asthma and myocarditis at

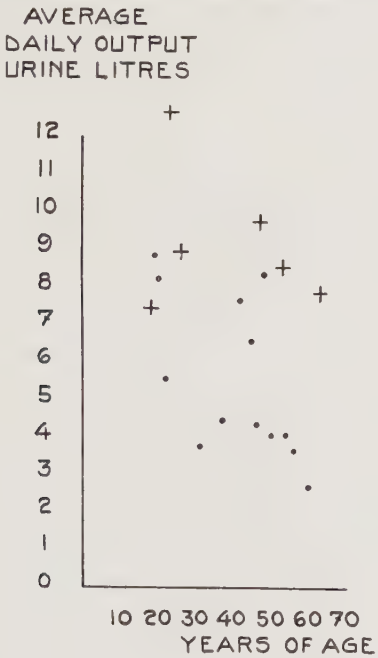


Fig. 10. Average daily outputs of urine from AH (dots) and J (+) patients.

the time of the investigation, while the younger one was generally healthy.

The above examples of variations within the pedigree all refer to the group AH. No clear differences have appeared between the few affected members of Pedigree J.

2. *Variations between groups AH and J.*

It is difficult to make reliable comparisons between the average intensity of the disease in the group AH on the one hand and group J on the other, because the J patients are so few. The diagram in fig. 10 shows the mean daily output of each adult patient in relation to his age. When the same patient

has been investigated at different ages, he is represented by several figures. The AH patients are indicated by a dot and the J patients by +. H: III: 14, for whom only one single daily output exists, has been left out. It can be seen that the patients fall roughly into two classes, one over the 6-litre level, and one below. All the J patients belong to the first group. It should be mentioned that only 4 J patients are represented. Two of these are relatively old, so that the difference cannot be explained by saying that the J patients belong to a lower age category.

The author has sought another expression for the same difference in intensity as follows. The mean of the average daily outputs was calculated separately for each group of patients, so that each patient is represented by one figure. In the case of B: VI: 34 and J: III: 9, who had been investigated more than once, the mean of the average outputs on each different occasion was first calculated. On the other hand, B: VII: 25, G: VI: 34 and J: III: 5 are represented by figures from the longer period of treatment, since these are more trustworthy than the average figure for two or three days. H: III: 14 has, as before, been left out, since the low figure for the only day he was under observation may be highly misleading. The omission of the figures for the shorter periods of treatment and for II: III: 14 causes throughout a decrease in the difference

Table 8.

Average daily outputs.

Group AH		Group J	
Patients	Outputs cc	Patients	Outputs cc
B: VI: 34	4,610	J: III: 1	7,870
B: VII: 25	4,370	J: III: 5	7,490
B: VII: 26	8,440	J: III: 9	9,190
B: VII: 61	6,630	J: IV: 8	12,720
B: VIII: 36	8,920		
C: VIII: 7	3,820		
G: VI: 34	5.640		
G: VII: 94	4,530		
H: III: 4	8.300		
	Mean 6,140		Mean 9,317

between the groups. The result of the comparison is shown in table 8. This line of approach, also, leads to results indicating that the disease in pedigree J is generally more intense. It should once again be stressed, however, that no definite conclusions can be drawn.

Finally a third expression of a varying intensity of disease between the two patient groups AH and J can be gathered from the course of those thirst tests which were made without pituitrin. Let us look, in the diagrams published below, at the section on susceptibility to pituitrin (figs. 12—24). The filled columns represent the amount of urine passed every 30 minutes in these thirst tests, and the unbroken curves represent specific gravity and chloride concentration.

The AH group (figs. 12—22) shows, more or less clearly, a tendency towards decreasing amounts of urine and rising specific gravity and chloride concentration during the process of the test. That is to say, these patients exhibit a tendency to the same defence against drying up as normal subjects show to a far more marked degree.

No such tendency can be detected in the two investigated J patients (figs. 23 and 24) during the time the thirst tests were made by the author. It is true that J: III: 9 emptied his bladder so irregularly that the amounts of urine are difficult to assess. Nevertheless, the curves for specific gravity and chloride concentration have a strikingly horizontal course. In a thirst test performed during an earlier stay in hospital, this patient emptied his bladder more regularly, and the amount of urine he passed during the 9 first half-hour periods formed the following series: 165, 144, 142, 147, 205, 158, 176, 178 168 cc/30 minutes. In the diagram for the patient J: IV: 8, the rigidity in the thirst test comes out very clearly. The volume of urine was as great at the end of the test as it was at the beginning. The curves for specific gravity and chloride concentration run horizontally.

Thus the AH and J patients seem to represent two different types of diabetes insipidus, which were also formerly recognized (Veil 1923, Depisch and Högler 1927; and others): one type

with a definitely coercive polyuria and another with a relative power of economizing the supply of bodily water.

Influence of fever.

According to the literature, the symptoms have sometimes been observed to abate or disappear in connection with fever. The author has systematically questioned all his patients on this point, but the anamneses have never contained observations of this kind.

The hospital observation of a small number of patients has

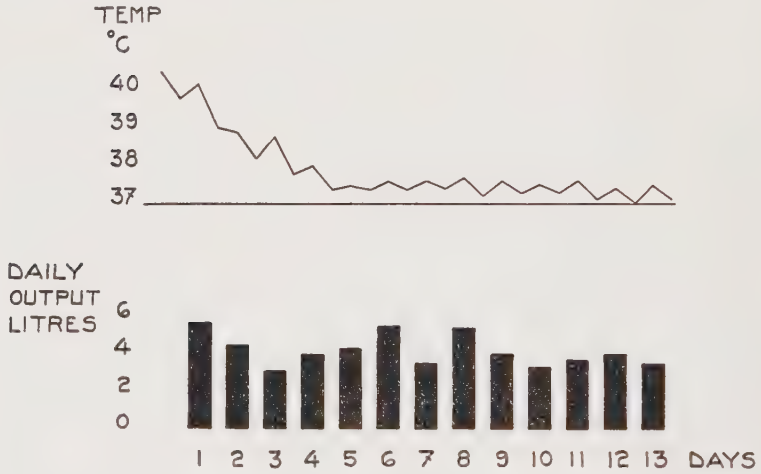


Fig. 11. B: VI: 34. Diuretic level during fever and a following afebrile period.

covered both febrile and afebrile periods. When dealing with the material from this angle, days when the lowest recorded temperature was 38.0° C or more were denoted febrile, while afebrile days were those when the temperature did not exceed 37.9° C.

Group AH: During his first stay in hospital in 1920 at the age of 42 years, B: VI: 34 had a moderate temperature for 2 days. On these days the daily output of urine reached higher values than at any other time during the treatment; this can be taken at least as an indication that there was no material

fall in the diuresis during the fever in this case. The same patient was again under observation during a fever 12 years later. Fig. 11 is a diagram showing — as an illustration — that the quantities of urine are not noticeably dependent on the temperature.

During treatment in 1908 for pneumonia, the patient G: VI: 34 yielded a mean daily output for 30 afebrile days of 5,840 $\pm$ 200 cc. During 5 days of fever, the mean was 4,500 cc, which figure is less than the first figure minus 3 times the standard error. However, a relatively large standard error naturally attaches to the 5-day period, so that the difference cannot be considered definitely significant. Furthermore, the patient has stated that, on admission to hospital (i.e. at the fever period), he was forbidden to drink so much, because at that time his diabetes insipidus had not yet been recognised, and drinking was thought to be bad for his pneumonia. During the fever period, therefore, he was constantly under relative debarment from water. However, this evidence was given after 35 years, though it was admittedly unsolicited and bore all the semblance of truth.

In Pedigree J, J: III: 1 has been under observation with complete daily outputs during 16 febrile days and 30 afebrile days. The difference between the means for these 2 periods is 270 $\pm$ 560 cc; that is to say, no real difference could be shown. J: III: 5 has been under observation during 9 febrile days and 7 afebrile days. The mean daily outputs were 9,360 and 7,510 cc respectively. Here the trend of the difference is towards greater diuresis during fever, but the standard error has not been calculated on account of the small number of observations. J: V: 3, finally, was under observation for 14 febrile days and 36 afebrile days. The difference between the means of the daily outputs is 90 $\pm$ 74 cc, — that is to say, quite within the random variation.

Summing up we can say that neither in group AH nor in group J does the author's material show any tendency towards an alleviation of the diabetes insipidus syndrome in connection with fever.

Reaction to posterior pituitary lobe extract.

As the tested members of group AH and the J patients differed in their reaction to posterior lobe extract, the author intends to describe these tests in some detail.

A possible way of investigating the posterior lobe effect would be to study the volume and specific gravity of the daily outputs of urine, but this is not feasible except when the observation period is fairly long; and the patients have not been available for such lengthy periods. In any case a better method seems to be to study, at short intervals, samples of urine obtained in the hours immediately following a hormone injection, since we know that the action of the posterior lobe extract describes a curve which rises and falls fairly rapidly. Patients have therefore been tested by submitting to the thirst test on two days, often consecutive, on the second of which they are given a dose of posterior lobe extract.

At the thirst test the patients were debarred from all liquids at 7 a.m., though they had been allowed to drink their customary amount during the night. Thirst tests when the diagnosis is uncertain are often started in the morning after debarment from water the previous night, but this procedure cannot be adopted in diabetes insipidus without causing the patient considerable distress. It is, moreover, not desirable to test the reaction to posterior lobe extract on the patient when he is in a dried-out state, since the effect of the extract comes out more clearly in a well-hydrated patient.

As the patients had often taken a drink just before 7 a.m. (it was not possible to achieve complete uniformity, on account of the varying habits as regards drinking at night) the actual test did not begin until 8 a.m. In choosing this time, the author calculated on getting the patients in an intermediate, 'well-watered' condition, but sought to avoid beginning the test with an actual water loading. From 8 a.m. on, the patients were made to urinate every 30th minute, being then instructed to empty their bladders as completely as possible. During the whole test, they were debarred from all water and food. The test was prolonged for as long as the patient could stand it without too much discomfort. Most patients faithfully sub-

mitted to a certain amount; on the other hand, they were never forced to undergo painfully long thirst tests. Only one patient of those published here can be assumed to have interrupted the test unnecessarily early on account of a disinclination to co-operate (C: VIII: 7). The tests usually lasted 5—6 hours. Those who reacted to the hormone generally continued the thirsting process for a longer time on the second test day.

The posterior lobe preparation used was Hypadrin, from the Swedish manufacturing firm of medical supplies Astra; with one exception this drug was given in the dose of 1 ml, injected subcutaneously at the beginning of the test. 1 ml corresponds to 10 I.U. In the 2 cases where the patients were refractory to the preparation, its effectivity was tested by giving the same dose, taken from the same packet, to a definitely susceptible patient. According to information from the firm, the ampules in any one packet are without exception manufactured and tested in the same batch.

Determinations were made on the half-hour urine samples for volume, specific gravity, and chloride concentration. The chlorides were determined solely in order to obtain an expression for the urine's concentration in addition to that provided by the specific gravity. They were selected from among other dissolved substances because they are easy to determine. The concurrent determination of specific gravity and chloride concentration gives a double check of the reaction to the posterior lobe hormone.

The results of the pituitrin tests are presented by the diagrams below. The columns represent the volume of the urine samples; those filled in are from the first test day, the blank ones from the second test day with pituitrin. As the 30-minute portions differed greatly in size from patient to patient, it has been necessary to vary the scale. One patient might produce about 500– 1000 cc per 30 minutes, another about 80—100 cc. A fixed scale would have rendered some diagrams unclear, and have caricatured others. The column diagrams can therefore not be used to compare different patients with one another, but only to illustrate the two different test days in the same patient.

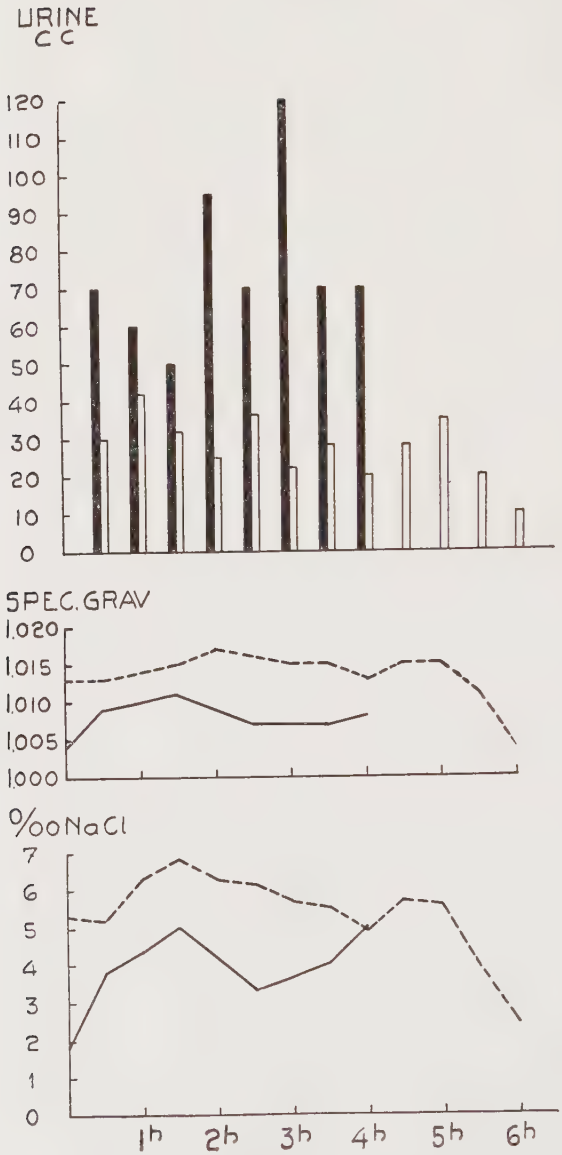


Fig. 12. B: VII: 25. Thirst tests without and with pituitrin. Filled in columns and unbroken curves represent the first test day without pituitrin, blank columns and broken lines the pituitrin test. On the 2nd test day the starting values for specific gravity and chloride concentration were already greater than those reached on the 1st day. On the 2nd day, therefore, the patient showed a lower diuretic level — his

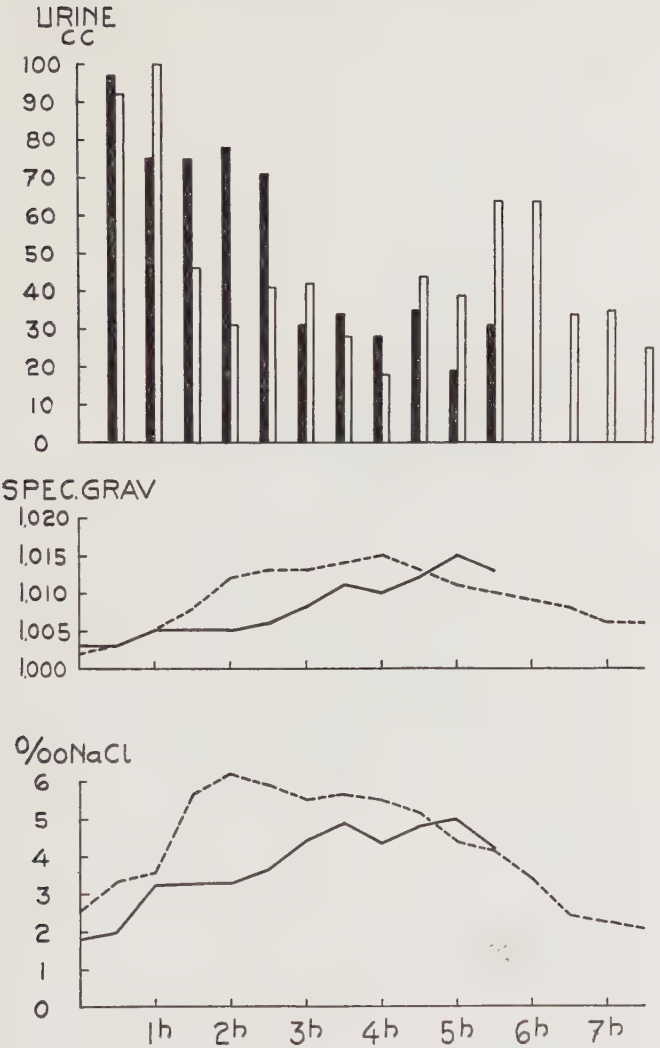


Fig. 13. B: VII: 26. Thirst tests without and with pituitrin. Plain reaction of typical kind.

diabetes insipidus syndrome was, generally, not very intense. A marked fall of the specific gravity and the chloride concentration after 5 hours can be taken to indicate that the antidiuretic effect of the pituitrin has ceased. The willingness of the patient to continue thirsting for 2 hours longer on the 2nd test day also indicates effect. The diagram gives no very strong proof of susceptibility to pituitrin, but nor can it be said to demonstrate lack of response.

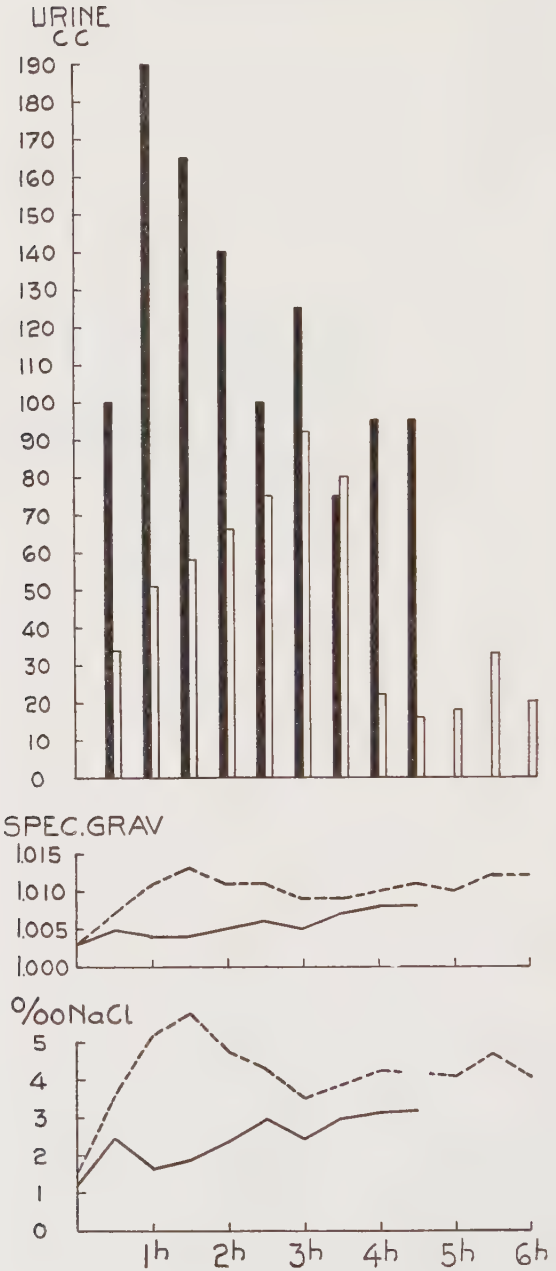


Fig. 14. B: VII: 61. Thirst tests without and with pituitrin. Plain reaction of typical kind.

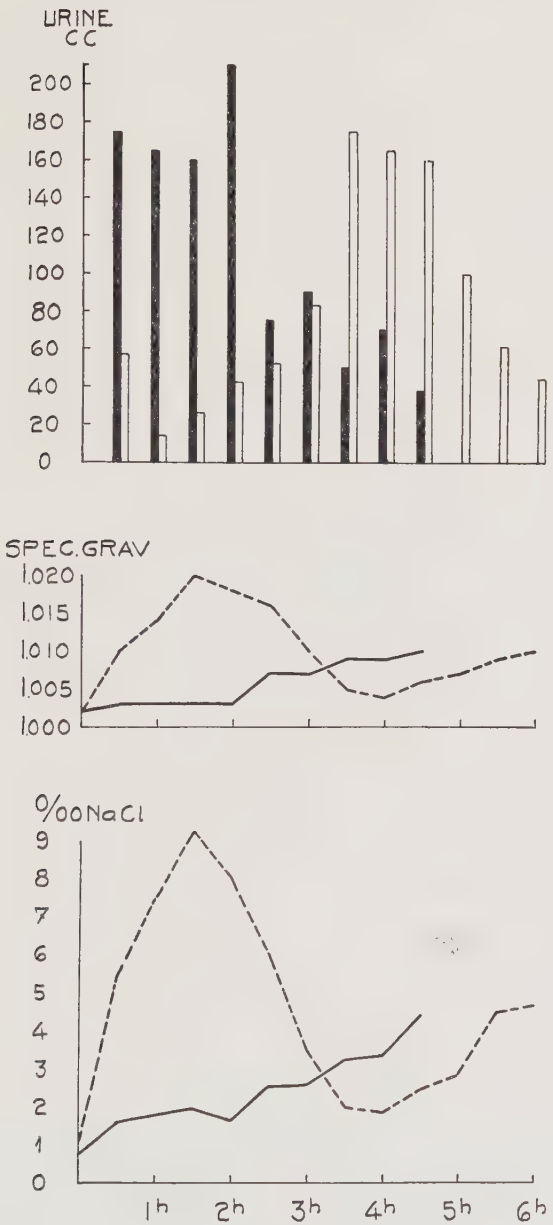


Fig. 15. B: VIII: 36. Thirst tests without and with pituitrin. Very marked reaction of typical kind.

Fig. 16. C: VIII: 7. Thirst tests without and with pituitrin. An oligophrenic man, who was averse to the investigation, and who on both days interrupted the thirst test after 2 1/2 hours. On the first day, moreover, he was unable to urinate after 30 minutes; the subsequent large portion of urine therefore represents 60 minutes. The curves obtained nevertheless seem to argue for reaction to the hormone, with reduction of the amounts of urine and a fairly plain rise in both specific gravity and NaCl concentration.

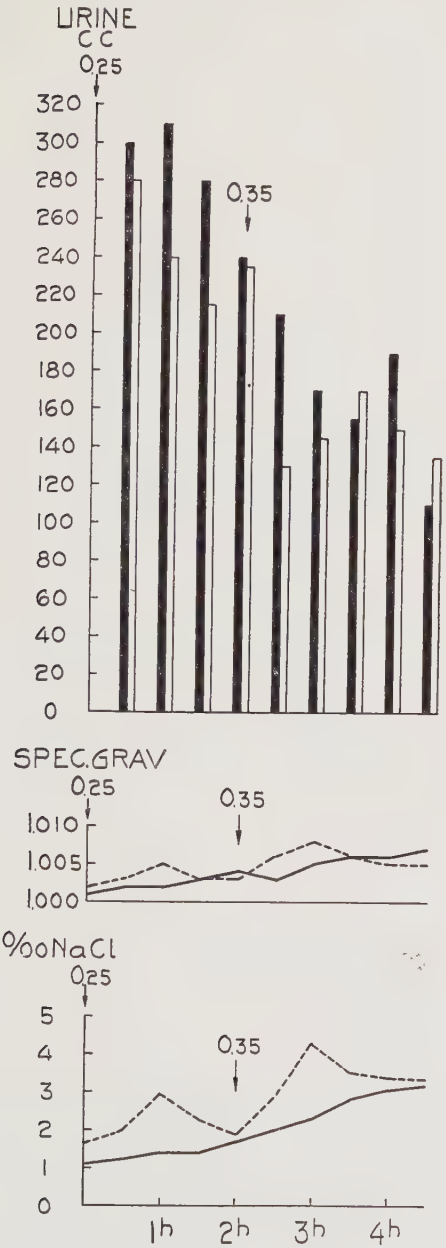


Fig. 17. E: VII: 13. Thirst tests without and with pituitrin. As the patient had hypertonia (blood pressure 260/140), it was too risky to take the usual dose of Hypadrin, owing to its pressor effect. Instead, the patient was given 2 small doses, 0.25 ml and 0.35 ml, at times given in the diagram. The plain effect of both these small doses demonstrates beyond question that the patient reacts to pituitrin.

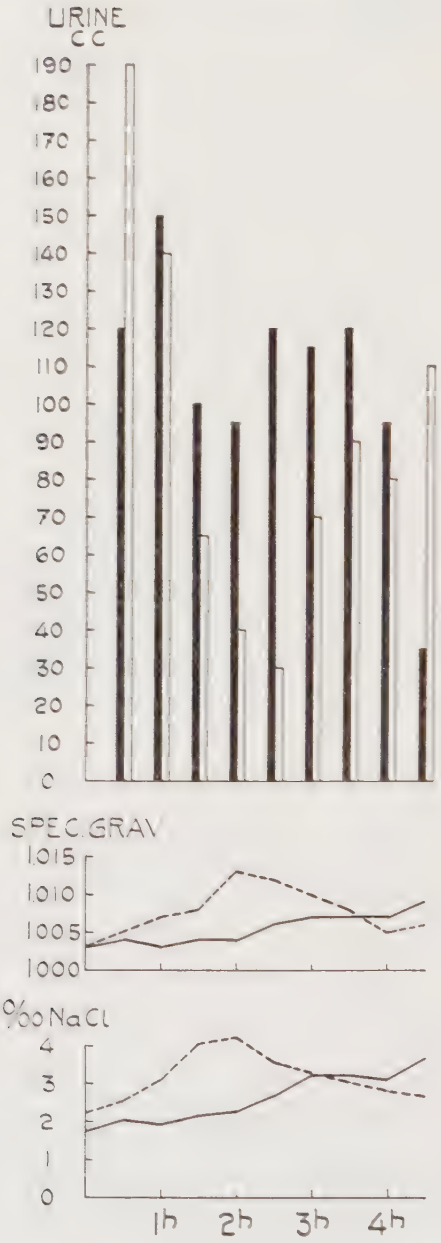


Fig. 18. E: VII: 16. Thirst tests without and with pituitrin. Plain reaction of typical kind.

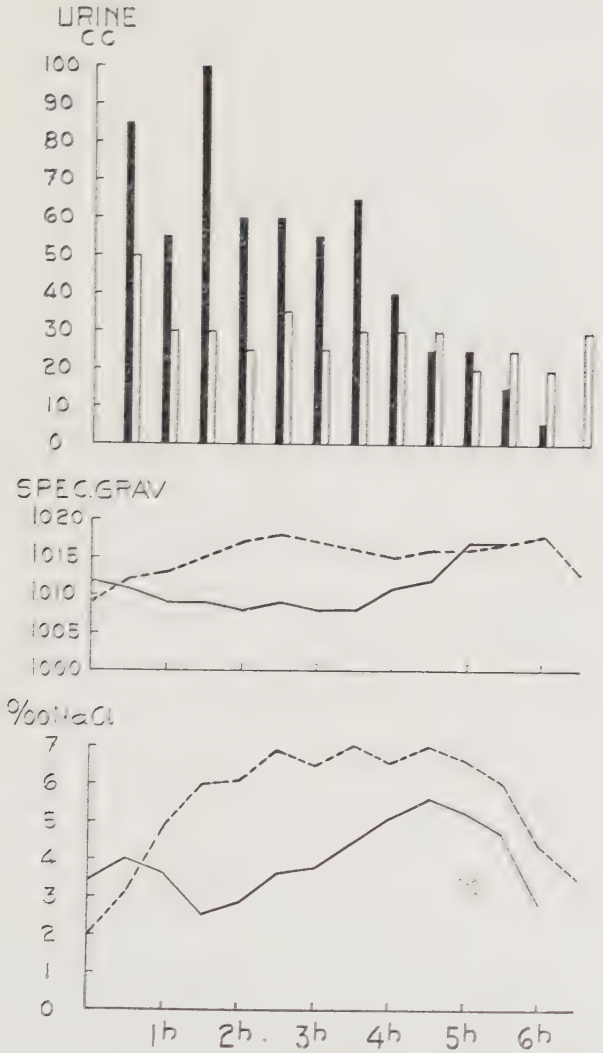


Fig. 19. G: VI: 34. Thirst tests without and with pituitrin. Plain effect of typical kind. In this patient the pituitrin test was mad three times. with very small variations in the result.

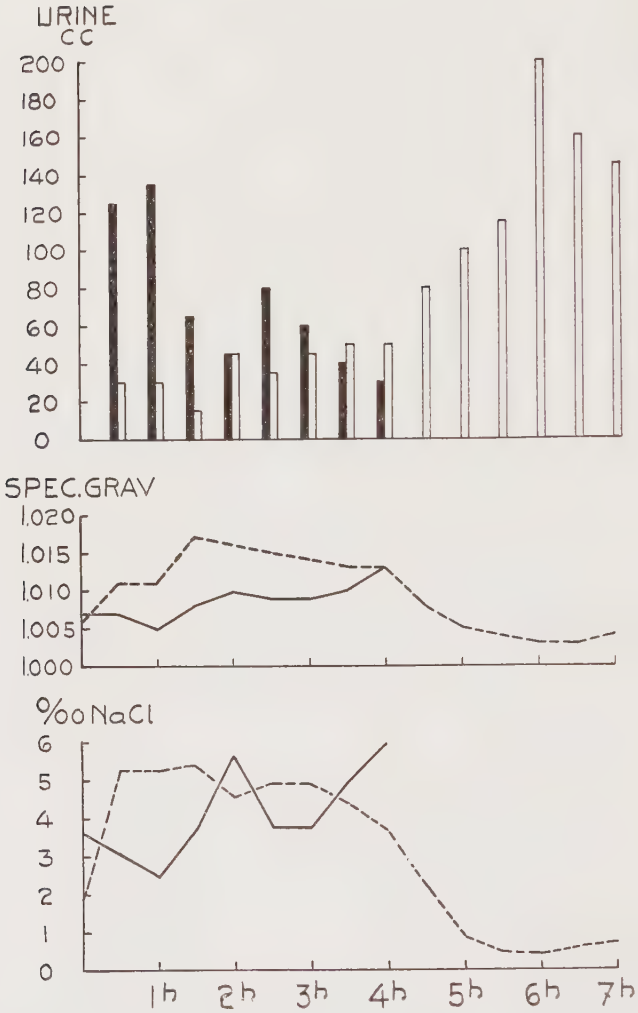


Fig. 20. G: VII: 94. Thirst tests without and with pituitrin. Plain effect of typical kind. The flow of dilute urine, in particular, markedly indicates the cessation of the anti-diuretic effect. The patient continued thirsting 3 hours longer on the 2nd test day.

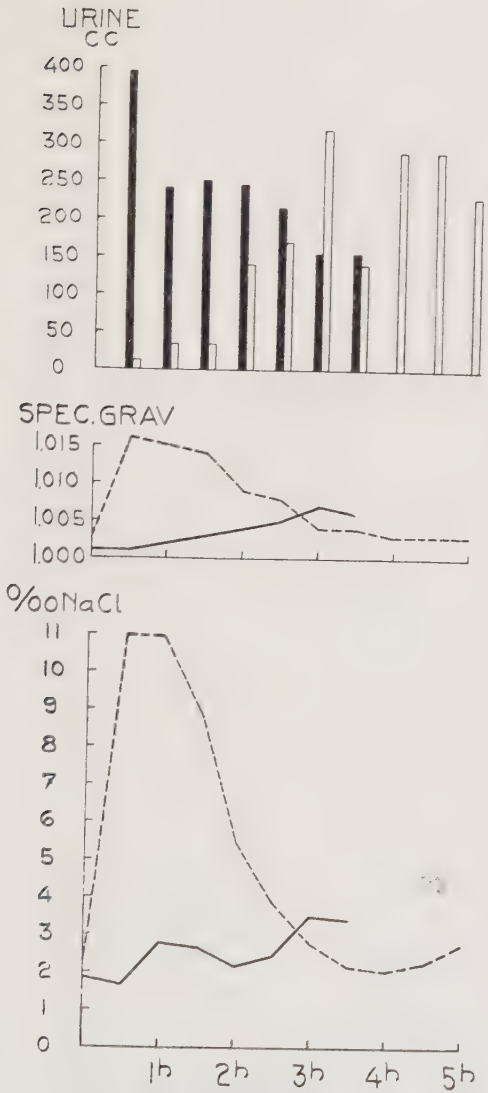


Fig. 21. H: III: 4. Thirst tests without and with pituitrin. Very marked effect of typical kind.

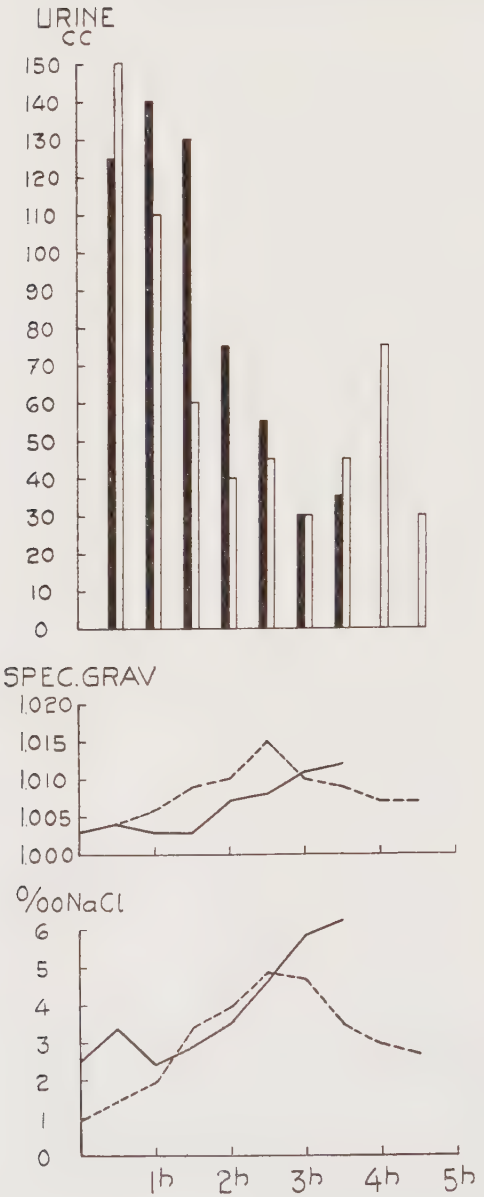


Fig. 22. H: III: 14. Thirst tests without and with pituitrin. The chloride concentration on the 2nd day was less than that on the 1st day. Some effect is nonetheless indicated in the course of the experiment, with first decreasing and then increasing amounts of urine, and rise and fall in the curves for specific gravity and chloride concentration. The patient went on thirsting an hour longer on the 2nd test day.

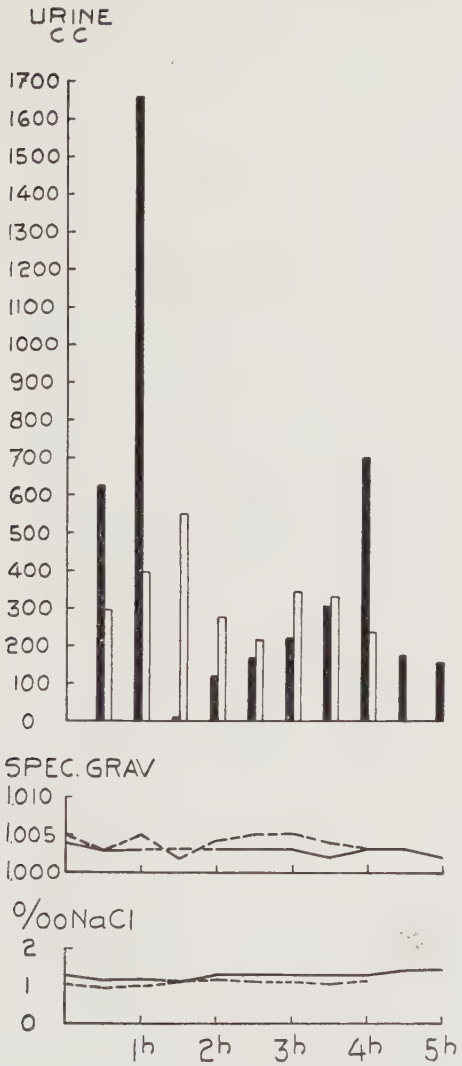


Fig. 23. J: III: 9. Thirst tests without and with pituitrin. The patient has obviously emptied his bladder incompletely on some occasions during the 1st test day. After fresh instructions, he empties it more regularly on the 2nd day. Neither in the amount of urine, nor in the specific gravity and chloride concentration can any effect of pituitrin whatsoever be traced. Above all, the sensitive method with chloride titration shows a striking rigidity, and practically complete agreement from one day to the other. — The Hypadrin ampule used was taken from the same packet as the one used in the pituitrin test on the patient G: VI: 34, fig. 19.

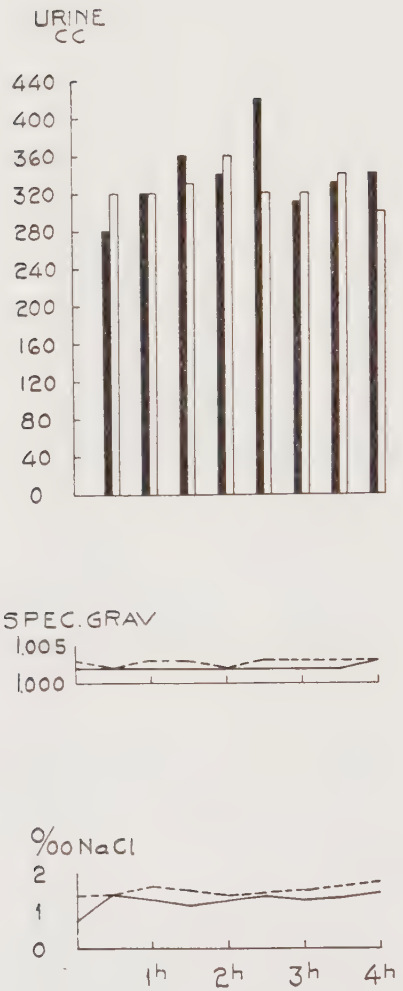


Fig. 24. J: IV: 8. Thirst tests without and with pituitrin. No effect from pituitrin whatsoever can be traced in the amounts of urine, the specific gravity, or in the NaCl concentration. — The ampule came from the same packet as the one used in the test on patient B: VIII: 36, fig. 15.

In the curves for specific gravity and chloride concentration, expressed as ‰ NaCl, the unbroken line denotes the first test day, without hormone, and the broken line the second test day with pituitrin.

The column diagrams do not include the urine passed at the start (denoted 0 o'clock), which does not represent any definite time. This portion was, however, used to determine the initial values for specific gravity and ‰ NaCl.

When no other time is given, the pituitrin was injected at 0 o'clock in the diagrams.

The typical effect of the posterior lobe extract is to lower the output of urine and raise the specific gravity and chloride concentration. After 4—5 hours, increasing quantities of urine and falling values for specific gravity and chloride concentration show the diuretic inhibition to be subsiding.

The diagrams demonstrate that the 2 J patients in the author's material differ from the AH group in that they do not show any reaction to pituitrin when tested with the procedure used. Posterior lobe preparations have been used on the same 2 patients on other occasions; in addition, a third member of the J pedigree has been tested with Hypadrin. Although the procedure on these latter occasions was not quite the one used by the author, it is naturally of importance to see the result in these tests, also, as the material in the J group is so small.

During a stay in hospital $^{17}/_{2}$—$^{6}/_{3}$ 1941, J: III: 9 was given different posterior lobe extracts for 11 days. The doses were fairly large, but were given only once daily, apart from one day when he received 2 injections. Fig. 25 shows the output of urine and the extracts given. The arrow marked 1 denotes 1 ml Tonephin Bayer, i.e. 5 I.U. The arrow marked 2 denotes '1 amp.' Pituitrin P.D. & Co, i.e. 5 or 10 I.U.[1], and that marked 3 indicates 0.5 ml Pressodrin Astra, i.e. 10 I.U. The mere diagram indicates that the daily outputs of urine were not affected. The mean for the 8 hormone-free days was 8,830 cc, and for the 11 days with hormone treatment, 8,450 cc.

[1] Pituitrin is obtainable in ampules of $^{1}/_{2}$ and 1 ml, so that it is not known whether he was given 5 or 10 I.U.

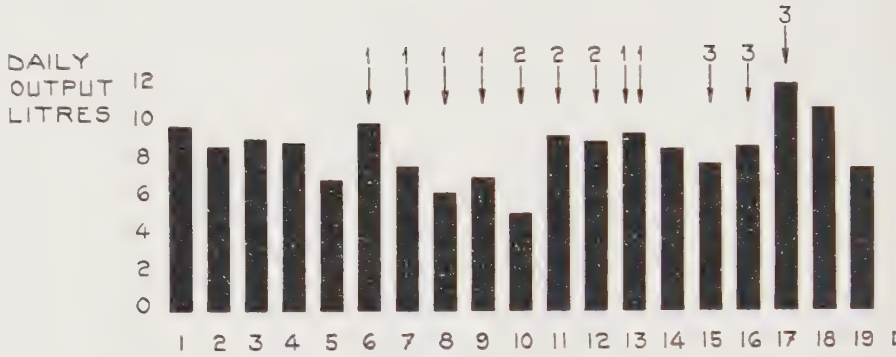


Fig. 25. J: III: 9. Urine daily outputs. The arrows indicate pituitrin doses: 1 = 1 ml Tonephin Bayer; 2 = '1 ampule' Pituitrin P. D. & Co.; 3 = 0.5 ml Pressodrin Astra.

The same patient was also tested on this occasion with a thirst test on one of the days during which he received 1 ml Tonephin. On this occasion no thirst test was made without hormone at a corresponding time of day. Chloride titrations were not made. The exact time when the Tonephin dose was given is not known, but according to information received it was in the morning. The results of the test are outlined in table 9. The great variations in the volume of the outputs, while the specific gravity was at the same time unchanged, indicates that the bladder was incompletely emptied. The figures for specific gravity have not been corrected for areometer errors, and can therefore not be compared with the author's figures for the same patient as shown in fig. 23. The uniform specific gravity in this test, also, implies that there was no effect from the Tonephin. It may be added that the patient never felt any subjective mitigation of thirst in connection with this posterior lobe treatment, whereas the subjective improvement was usually very marked in the patients who reacted to the hormone.

J: IV: 8 was, at the age of 9 years, in the Children's Clinic of the Academic Hospital, where he was tested with posterior lobe extract in the form of pituitrin Parke, Davis & Co. He weighed 25 kg, and received the dose of 0.5 ml (= 5 I.U.) during 2 consecutive days; this is a large dose. Fig. 26 shows that the daily output of urine was not markedly affected.

Table 9.

J: III: 9. Thirst test under influence of pituitrin.

Time	Urine cc	Specific gravity
8 a.m.	170	1.004
8.30	180	1.005
9	200	1.005
9.30	190	1.004
10	210	1.004
10.30	120	1.004
11	1000	1.004
11.30	930	1.003
12 noon	950	1.003
1 p.m.	130	1.003
2	530	1.003
3	740	1.003
4	390	1.004
5	430	1.003
7	160	1.004
8	460	1.004
9	470	1.004
10	120	1.004
11	460	1.003

A 3rd patient from the pedigree J, namely J: V: 3, was tested for his reaction to Hypadrin at the Medical Department of the hospital 'Kronprinsessan Lovisas Vårdanstalt' in Stockholm. At the time of the investigation the patient was 2 $^{1}/_{2}$ years old and weighed 7.200 gm; he was thus very backward in his general development. The dose used was 0.1 ml (= 1 I.U.). Thirst tests were made in the morning after debarment from water all the previous night. Table 10 shows the results of the tests.

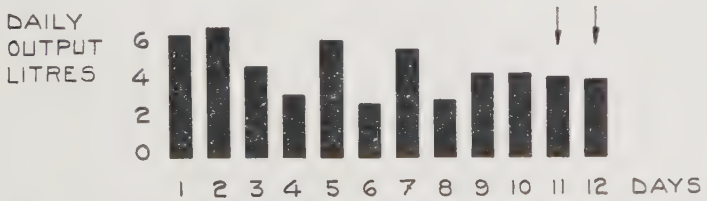


Fig. 26. J: IV: 8 at 9 years of age. Urine daily outputs. The arrows indicate 0.5 ml Pituitrin P. D. & Co.

Table 10.

J: V: 3. Thirst tests. I = without influence of pituitrin. II = 0.1 cc "Hypadrin" injected 8 a.m.

Time	Urine cc		Specific grav.		‰ NaCl	
	I	II	I	II	I	II
7 a.m.	100	130	1.005	1.006	1.97	1.30
9	90	30	1.005	1.009	3.46	1.95
10	50	—	1.007	—	4.26	—
11.30	—	30	—	1.014	—	3.01
12 noon	5	—	—	—	—	—

In this case, the tests were made with the patient in a dried up state, due to the debarment from water the previous night, and therefore under different conditions than those used by the author. The table seems to show that the specific gravity reached higher values in the pituitrin test than on the foregoing day. A striking fact is, however, that the chloride concentration is, at the same time, lower. On the day of the first test the highest specific gravity was 1.007, which corresponds to 4.26 ‰ NaCl. In the Hypadrin test the specific gravity reaches 1.014, but the NaCl content does not exceed 3.01 ‰. An NaCl content of 1.95 ‰ has been found with a specific gravity of 1.009 — that is to say, a plainly lower value than the NaCl content when the specific gravity on the first test day was 1.005. Even if there is no absolute parallelism between the specific gravity and the chloride concentration, the discrepancies were not great in the author's investigations.[1] Of the two methods, chloride titration and determination of specific gravity, the former is without doubt by far the most sensitive. On these grounds it seems likely that the table's figures for specific gravity on the day of the second test are too high.

The possibility of influencing this patient with pituitrin can also be studied in his daily outputs of urine, as he was for 12 days treated with injections of the hormone. On 11 of these days he received one daily injection of 0.1 ml Hypadrin and on 1 day he had 2 such doses. The mean measured daily output of urine during these 12 days was 710 ± 21 cc, and

[1] Cf., however, the diagram for the patient K: III: 7, fig. 29.

during 50 days without pituitrin, 740 ± 31 cc. The difference of 30 ± 38 cc is less than one standard error. (The patient, who was backward in his development, did not yet control his urination. The urine was collected in a container; this always involved certain losses. Thus, the daily outputs are not absolutely complete, but this error affects all the daily measurements at random, and does not therefore involve any systematic error.)

Discussion.

Thus, it has been shown that the patients in group AH are, with the testing technique used by the author, always more or less susceptible to pituitrin, or at all events never obviously refractory. The only 2 investigated patients from the pedigree J have proved totally refractory when investigated with this method. Nor did these same 2 patients show any signs of reaction to the posterior lobe extract in other clinical tests. A 3rd J patient, who was investigated with posterior lobe extract at another hospital and with a different technique from that of the author, cannot be used for a direct comparison, but the results of the tests nevertheless suggest that this case, too, is refractory rather than otherwise.

The author is aware that 'refractory' in this context only means that the patient did not react to the doses used and in otherwise similar conditions. Perhaps even the J patients would have reacted to larger doses. However, it is difficult to use larger doses on man, on account of the secondary effects on the smooth musculature and the vascular system. When E: VII: 13 was tested, one quarter of the usual dose was given, and even so the effect was plain. The dose of 1 ml can therefore not very well be near the lower limit of what is effective in the pedigree AH.

Needless to say, it is difficult to draw conclusions from comparisons between groups of patients when one of them only comprises 2 (or if you will, 3) investigated cases. And, indeed, if quantitative differences had been in question, the author would have refrained from drawing any conclusions whatsoever. With the methods used, however, the differences in

question are of an absolute kind: refractory — susceptible. It does not seem likely to the author that it is by chance that the only 2 patients in the material who do not react to pituitrin happen to be uncle and nephew, and that another probably refractory patient belongs to the same family. In point of fact, the most reasonable explanation of their lack of reaction to the posterior lobe extract is that the groups AH and J derive from different mutations. Another way of saying this is that the sex-linked diabetes insipidus appears in a series of multiple allelism.

Investigation of the colour sense.

In questions of a gene localized in the sex chromosome, it is interesting to see whether the patients show other sex-linked characters and disorders, by which linkage and crossing-over could be demonstrated.

No particular search need be made for haemophilia and a number of rare neurological diseases inherited via the sex chromosome. It is obvious that none of the author's patients can have shown these conditions. On the other hand, a test of the colour sense is necessary before defects can be ruled out. In the following case the colour sense was investigated at the Ophthalmic Clinic of the Academic Hospital.

Group AH	Group J
B: VII: 26	J: IV: 8
B: VII: 61	
B: VIII: 36	
C: VIII: 7	
G: VI: 34	

All those investigated proved to have a normal colour sense.

Patho-anatomy.

The author's material does not throw much light on the question of the patho-anatomy behind hereditary diabetes insipidus. Only in one single case (J: III: 1) was an investigation of the central nervous system made, and even here the results were meagre, on account of complicating diseases and technic-

ally unfavourable circumstances. As, however, the chances of investigating these patients are so extremely rare, there seems to be justification for describing every observation.

J: III: 1 died in 1936 at the age of 63 years from an ascending infection of the urinary tract. Before death there had been several months' illness with remittent high fever. The clinical diagnosis was: Cystopyelitis (main cause of death), diabetes insipidus, myocarditis chronica, scurvy. The following report was issued from the Pathological Institution of the University of Upsala on the investigated parts of the central nerve system and hypophysis:

'The hypophysis and parts of the mesencephalon were fixed about 15 hours after death and embedded in paraffin. Horizontal sections from near the centre of the hypophysis were stained according to Kraus, Wallart and Houette, Crooke, with haemotoxylin-eosine, and according to Bodian, in the last case after treatment with pyridine according to Szatmari. The brain sections were stained according to Nissl.

The anterior lobe of the hypophysis showed no certain pathological changes (no differential count was made). The posterior lobe presented a remarkably small number of silver-stained fibres. It is uncertain whether the finding can be considered pathological, in view of the long interval between death and fixation.

In the tractus opticus and neighbouring parts of the hypothalamus, and in the lateral thalamus, there were fresh encephalitic foci, some of them small abscesses. There was proliferation of astroglia in the lower part of the third ventricle's walls in the region of the nucleus paramedianus, which latter did not appear distinctly. The ventro-lateral part of the nucleus supraopticus was not unquestionably changed; the ventro-medial portion showed glia proliferation. One of the groups in the nucleus tuberis had been encountered by the section, and was normal.'

Thus, the investigation has shown a reduction in the number of silver-stained fibres in the posterior pituitary lobe, a reduction which, on technical grounds, cannot be assessed. The changes in the hypothalamus are certainly exogenous, at any rate some of them.

A future aim of great importance will be to investigate histologically specific organs from as many members of the

groups AH and J as possible. It is conceivable that a comparison between a number of investigated patients from these two groups might lead us nearer to solving the problem of resistance to pituitrin.

CHAPTER 6.

Sex-linked genes. Clinical viewpoints. Conductors.

The material.

Those parts of the sex-linked pedigrees which were accessible direct or by means of others' testimony contained 40 certain conductors, determinable as such by their position in the pedigrees — that is to say, they had been either mothers or daughters of affected men. They fall as is shown in table 11.

Table 11.

Conductors from pedigrees showing sex-linked inheritance, divided according to the reliability of the results.

Group	Number of cases	At the beginning of the investigation			
		dead	living		
			Emigrated or otherwise not reached	Interviewed	Clinically investigated
AH	36	12	3	12	9
J	4	1	—	1	2
Total	40	13	3	13	11

Anamnesis.

The author has been unable to study the conductors in hospital in more than 11 cases. Apart from a possible slight increase in their water consumption and their urine, these women are normal, and regard themselves subjectively as quite

healthy. For a good idea of their average daily output of urine, it would be necessary for them to stay in hospital a relatively large number of days. The conductors who agreed to hospital investigation for some days were subjected to a water loading and thirst test, so that it is not often that these days yield reliable information as to the habitual daily output of those concerned. A fairly large number of the conductors could not be persuaded into hospital observation, the author instead visiting them for systematic questioning. As regards the phenomenon diabetes insipidus gravidarum, no conditions for an objective verification offered within these pedigrees: none of the conductors were pregnant during the time covered by the investigation. The author has therefore had to resort entirely to anamnestic data on this head.

The habitual daily output.

The questions put to the conductors were these:

Do you drink more water than people usually do?

Have the persons round about you noticed and commented on the fact that you drink especially much? Brothers and sisters? Husband? Friends?

Do you wake up at night to drink? To urinate?

These questions were naturally often complemented by others in the individual case. Those who drank strikingly much were asked how much, and so on. As far as possible, the author has also tried, by enquiring among the nearest associates of the patient, to obtain objective support for the anamnesis she herself gave. The parent outside the pedigree and other definitely non-gene-bearing near relatives have, more than other witnesses, often made psychologically valuable additions to the anamnesis. It is unfortunately impossible to give a concise and comprehensive account of this objective anamnesis. The author has always striven to avoid a suggestive manner, and tried to put the questions in a method conformable with good witness psychology.

Table 12 gives the conductor's anamnesis as to the habitual state (i.e. when not pregnant). Of 24 conductors, the anamnesis shows 13 to have certain symptoms of diabetes insipidus, and

Table 12.

Anamnesis of 24 conductors.

Conductor	Strikingly thirsty	Nightly water consumption
A: VI: 1	—	—
B: VI: 31	+	—
B: VII: 58	—	—
B: VIII: 21	—	—
B: VIII: 22	—	—
B: VIII: 23	—	—
B: VIII: 41	—	—
C: VII: 4	+	at least once a night
C: VIII: 8	+	—
E: VII: 4	+	—
E: VII: 5	+	sometimes
E: VII: 6	+	sometimes
E: VII: 7	+	—
E: VIII: 14	+	—
F: VII: 1	—	—
G: VI: 31	—	—
G: VIII: 60	+	1—3 times a night
G: VIII: 61	+	once a night
H: II: 2	+	sometimes
H: II: 5	+	1—2 times a night
H: II: 7	+	once a night
J: III: 8	—	—
J: IV: 6	—	—
J: IV: 10	—	—

of these 13, 8 drink more or less regularly during the night. In view of the very considerable factors of uncertainty which always attach to anamnestic data collected in this way, the author has attempted to procure a normal material by putting the same anamnestic questions to presumably healthy women. The procedure is, in principle, the same as that used by Andreassen (1943) when investigating conductors for haemophilia.

The following questions were put to 105 probationers:

Do you consider yourself to suffer from remarkably severe thirst, and do you drink more water than what is normal or customary? Has this been commented on by friends or

relations? 102 of the 105 answered No, 3 answered Yes. These 3 were also asked if they used to drink at night, and all replied they did not.

Table 13.

Comparison between conductors and presumably normal women as to striking thirst.

	Striking thirst?	*Number*	*Percentage*
Conductors	Yes	13	54.2 ± 10.2
	No	11	45.8 ± 10.2
	Total	24	100.0
Presumably normal women	Yes	3	2.9 ± 1.6
	No	102	97.1 ± 1.6
	Total	105	100.0

Table 13 outlines the results. If the standard error of the difference is calculated in the ordinary way, the difference is found to amount to 51.3 ± 10.3 %, which is thus significant. In other words, it is not an accident that the frequency of affirmatives is greater among the conductors than among the presumably healthy subjects.

The 2 categories do not have quite the same psychological starting-point, and it may be that the occurrence of diabetes insipidus in their family has made the conductors specially aware of their water consumption, and that it is on these grounds that affirmatives preponderate among them. This source of error might be dealt with by extending the question to the sisters of the conductors. This group must contain a large number of non-gene-bearers, and consequently the frequency of affirmatives ought to be lower than in the pure conductor group — if, that is to say, the suggestive factor does not play much part. (Cf. Andreassen 1943.) However, this control occurred to the author too late, and no systematic questioning of this kind has as yet been made.

Diabetes insipidus gravidarum.

Conversation with the diabetes insipidus sufferers on their family anamnesis led at an early stage to spontaneous accounts

of women who were habitually healthy, but who, during pregnancies, showed symptoms of the thirst disease of an intensity comparable with that of the affected husbands. In certain branches of the large pedigree, this phenomenon had been noticed, and aroused much curiosity. In a few cases vivid descriptions were given of how the disease arose during the pregnancy of women now dead, and how it disappeared a short time after childbirth. The author has therefore systematically gone into this phenomenon with all the conductors who have had children. Table 14 outlines the answers.

Table 14.

Occurrence of diabetes insipidus gravidarum in conductors.

Conductor	Number of pregnancies	Diabetes insipidus in pregnancies
B: VI: 31	5	severe
B: VII: 58	3	—
C: VII: 4	5	severe
C: VIII: 8	1	distinct
E: VII: 4	2	distinct
E: VII: 5	3	severe
G: VI: 31	4	—
H: II: 2	3	in 2nd pregnancy distinct in 3rd severe
H: II: 5	2	severe
H: II: 7	2	—
J: III: 8	4	—
J: IV: 6	1	—

The second column includes only full-term or almost full-term pregnancies, since the phenomenon belongs to the last part of this condition, and thus cannot be expected to appear in abortions. Thus, of 12 conductor mothers, 7 have given a convincing description of diabetes insipidus gravidarum, a description that has often been most vivid. Repeated drinking during the night occurred regularly in these cases. The consumption of water amounted to several litres. One of the women, H: II: 2, clearly stated that she was not troubled by this disorder in her first pregnancy, had it plainly the second

time, and severely the third time. There are 3 within the group AH who say that they have not experienced the phenomenon. Of these, one was suffering from advanced senility (G: VI: 31) at the interview, and died shortly afterwards; her testimony must be regarded as highly unreliable. In one case, on the other hand, the evidence is particularly reliable, i.e. B: VII: 58. Her mother, who had suffered from pronounced diabetes insipidus gravidarum, had often said that the phenomenon might manifest itself during the pregnancies of the daughter. The subject came up between mother and daughter when the latter was pregnant, and she therefore claims to be able to state with certainty that she did not suffer any material increase of thirst during any of her 3 pregnancies. The third case also seems fairly trustworthy; it is that of a woman with 2 children (H: II: 7). Neither of the 2 J women interrogated had any experience of this phenomenon.

The assessment of the anamneses of diabetes insipidus gravidarum also calls for a certain amount of caution, since — as the survey of the literature shows — it is not unusual for women nearing the end of pregnancy to show a certain increase in their water consumption. To obtain a normal material for the anamnesis as regards this phenomenon, the author took a certain day and put the following question to all mothers in the Medical Clinic of the Academic Hospital: Have you been unusually thirsty during one or more of your pregnancies? (Note that it is thirst that should be enquired into, and not the urination frequency, in which, as is known, pregnant women show a fairly regular increase contingent on other factors besides the amount of urine.) The material for comparison purposes came to consist of 50 women, who had together produced 207 children, i.e. an average of 4.1 children per woman. In the conductor group the average number of children was 2.9. Thus, as the control material had undergone more pregnancies, and as the phenomenon increases in strength with the number of pregnancies, the number of children favours the occurrence of the phenomenon in the control material. The interrogated women provide a suitable material for comparison purposes in that they are of very different ages,

and were not all pregnant at the same time, conditions also obtaining in the conductor group. The results are shown in table 15.

Table 15.

Comparison between conductors and presumably normal women as to symptoms during pregnancies.

	Increased thirst in pregnancies?	*Number*	*Percentage*
Conductors	Yes	7	58.3 ± 14.2
	No	5	41.7 ± 14.2
	Total	12	100.0
Presumably normal women	Yes	2	4.0 ± 2.8
	No	48	96.0 ± 2.8
	Total	50	100.0

The difference in the frequency of affirmatives is 54.3 ± ± 14.5 %, that is to say, it falls outside the limits of random variation. If — as is conceivable — the 2 interrogated J women did not just happen to answer negatively, and if the calculation is consequently to be made solely on the material in the AH group, the frequency among the conductors then becomes $^{7}/_{10}$, i.e. 70 ± 14.5 %, which increases the difference.

Finally, it is probably overdoing the caution to equate the 2 affirmatives in the healthy group to the description of diabetes insipidus gravidarum given by the conductors. These affirmatives came from 2 young women who had just been confined. The increase in their thirst had been plain. One of them had drunk during the night, to the extent of 1 glass a night during the last few months. On the other hand, a daily consumption of several litres of water was unknown to both these presumably healthy women.

The material also contains 16 heterozygote women, whom the author has not contacted personally. Of these, 13 are dead, 2 emigrated to America, and the last eluded investigation for other reasons. Evidence about 15 of these has been received from fairly close relations, who knew them well and who had generally lived with them — parents, children or sibs. One testimony is weak, being given by cousins on someone long

since dead (G: VI: 14). Only in 2 cases of these 16 did the relatives report abnormal thirst in the subject in question (E: VIII: 16 and G: VI: 13); the latter used to drink some time during the night. 10 of the 16 had been pregnant. In 2 cases the relations submitted a very convincing anamnesis of diabetes gravidarum (G: V: 8 and E: VI: 3), but in 8 cases they had not heard this complaint mentioned. The anamneses of the relatives can be looked upon as fairly reliable as regards positive observations, but are, on the other hand, obviously very untrustworthy as regards absence of symptoms. This is a natural indication that the slight or transitory symptoms of the heterozygote women did not make such a deep impression as the pronounced and chronic disorder of the men, and consequently did not enjoy the same prominence in the family tradition.

Of the 16 conductors testified to by their relations, only one comes from the pedigree J, i.e. the woman J: II: 1, d. 1929. Information about her has been given by a son and a daughter. According to them she did not have any symptoms normally; nor did she show any abnormal thirst during her 13 pregnancies. The testifying daughter, J: III: 8, was a 12-year-old living at home when her mother had her last child. It is therefore fairly likely that this daughter would have known about the conspicuous phenomenon diabetes insipidus gravidarum if her mother had suffered from it.

Besides those who can be determined as certain heterozygotes, these pedigrees also contain a number of possible conductors; i.e. all daughters of heterozygotes who have not had affected sons and thereby been relegated to the group of certain conductors. It is to be expected that this group, too, would contain a number of women who had vague symptoms betokening their heterozygotism, or who contracted diabetes insipidus when pregnant. The author has not interrogated these women consistently. In some cases, however, it has been revealed that a number of women in this category drink a great deal. H: III: 3 gave very clear information: Towards the end of her 3rd pregnancy she was very thirsty and had to drink several times a night. During the day she drank by

the litre. Nothing like this had happened during her 1st and 2nd pregnancies. Her abnormal thirst disappeared at partus. On this information, this woman can with a high degree of probability be denoted a conductor, although she has not as yet borne any affected sons.

Objective investigation results.

Daily outputs of urine.

The daily outputs of the clinically investigated heterozygotes can rarely be used as an indication of their habitual diuresis, since water metabolism tests were made during the few days they were observed in hospital. In a few cases, however, it has been possible to measure the amount of urine without disturbances of this kind. In a further very small number of cases, the conductors measured their urine in their homes. For this the author chose such patients as appeared reliable and willing to co-operate. They were carefully instructed how to make the measurement so that the amount measured should correspond to 24 hours. The measurements in the home were usually made over 2 days; in a few cases they were made only over one. The author is aware that these measurements, which were made without control, may involve

Table 16.

Conductors, daily output of urine.

Conductor	Number of observation days	Average output in cc
B: VII: 58	2	1,700
C: VII: 4	1	2,150 [1]
E: VII: 6	2	2,750
E: VII: 7	2	3,400
F: VII: 1	1	1,000 [1]
G: VIII: 60	2	2,550
G: VIII: 61	2	2,650
H: II: 2	1	1,800
H: II: 5	1	3,000 [1]
H: II: 7	1	2,500

[1] Controlled in hospital.

very large errors. Nevertheless, they provide information which in some cases supports the presence of mild polyuria, and they are recapitulated here, in table 16, in the absence of other and more certain results.

Power of concentration.

The most important thing in the clinical investigation of those conductors agreeing to hospital observation has been to get an idea of their powers of concentrating urine. This knowledge can be gained with the help of thirst tests. The dilution function should also be tested, to ensure that a possible deficiency in the power of concentration is not a sign of renal rigidity such as it manifests itself in kidney disease. The author has therefore elected to use the customary Volhard method with water loading and subsequent thirst test, the whole investigation taking 24 hours. This provides the possibility of comparison with normal values, which are common knowledge in this routine investigation.

Just as it is impossible to arrange very long thirst tests on male diabetics without discomfort to the patient, so may it be difficult to maintain consistent debarment from water in those women with plain signs of diabetes insipidus. For this reason it has been necessary in some cases to give small additions of water even during the thirsting phase of the test. These deviations from the strict thirst test are given for each separate case in the tables of the tests, to be found at the end of the book. As far as possible, the conductors involved have been persuaded to try and manage without water. They were allowed to suck small pieces of ice to mitigate their discomfort, and were often given a sleeping draught (of the barbituric type) at night, to obviate a premature interruption of the test. In the case of those investigated in hospital, the author has always made a special enquiry about any illnesses they may have had with albumin in the urine, or other signs of kidney disease. The state of kidneys and vascular system has been investigated according to the customary routine: examination of urine albumin and sediment, N.P.N., measurement of the blood pressure and a physical examination of the heart; in

some cases electrocardiograms were taken as well. In some cases, given separately, there was a test of the renal function with clearance investigations.

Table 17 shows the lowest and highest specific gravity of the water metabolism tests, and the values for blood pressure and N.P.N. The lowest blood pressure value shown by the hospital records has been taken. No anamnesis of those investigated showed kidney trouble. All had urine free from albumin and with normal sediment.

Table 17.

Conductors, clinical results.

Conductor	Age in years	Lowest spec. gravity	Highest spec. gravity	Blood pressure	N. P. N. mgm %
B: VI: 31	68	1.002	1.019	190/100	43
B: VIII: 22	20	1.001	1.031	125/80	35
B: VIII: 23	14	1.002	1.029	120/70	29
C: VII: 4	61	1.003	1.015	210/115	30
C: VIII: 8	26	1.003	1.018	140/80	27
F: VII: 1	38	1.001	1.024	125/90	28
G: VIII: 60	17	1.000	1.029	135/75	31
G: VIII: 61	15	1.001	1.028	130/70	29
H: II: 5	50	1.002	1.023	170/95	35
J: IV: 6	30	1.001	1.014	110/75	34
J: IV: 10	12	1.001	1.019	130/80	40

The table shows that the dilution function of all the investigated subjects was normal. Following Secher (1934) 1.003 and below was considered normal here. In conformity with the wide practice, Secher takes the lower limit for normal concentration in water and thirst tests to be a specific gravity of 1.025. On this criterion 4 of the investigated subjects have normal powers of concentration (B: VIII: 22, B: VIII: 23, G: VIII: 60 and G: VIII: 61). Nowadays, however, the limit is often set somewhat lower, and the author is therefore not inclined to designate as pathological the 2 cases (F: VII: 1 and H: II: 5) who approach the figure 1.025. The remaining 5, whose highest specific gravity does not amount to 1.020, must be considered to have distinctly inadequate powers of concentration.

After the objective investigation results have been described, the 5 conductors with inadequate concentration from table 17 deserve special discussion.

B: VI: 31, 68 years, maximal specific gravity 1.019. A woman who was treated for hypertonia, and who, at the investigation, had a blood pressure of 190/100. Her creatinine clearance showed a lowered value: 69 cc/min. On admission she had slight edema of the ankle. This is sufficient cause in itself to prevent any conclusions being drawn from the result of the investigation. She belongs to that group of conductors whose anamnesis point to slight diabetes insipidus, and who had had diabetes insipidus gravidarum.

C: VII: 4, 61 years, maximal specific gravity 1.015. A woman with plain hypertonia (210/115). No edema could be demonstrated. The creatinine clearance gave a rather low value (88.9 cc/min.). This woman had the clearest anamnesis of diabetes insipidus of any within the conductor group, with a nightly consumption of water since childhood. On one day and night when the thirst test was made without water loading, the output of urine amounted to 2,150 cc. It seems likely that her deficient powers of concentration are an indication of her diabetes insipidus gene.

C: VIII: 8, 26 years, maximal specific gravity 1.018. Had no anamnesis for renal disease and has normal blood pressure and normal creatinine clearance, namely 135 cc/min. Her diabetes insipidus gene is the only available explanation for the insufficiency in concentration.

J: IV: 6, 30 years, maximal specific gravity 1.014. Showed no signs of kidney disease. Had normal blood pressure and no edema. Had great difficulty in standing the debarment from water, and lost 1.7 kg during the test. The gene for diabetes insipidus is the only available explanation of her inadequate powers of concentration, but the investigation was not complete.

J: IV: 10, 12 years, maximal specific gravity 1.019. No anamnesis for kidney disease. Normal blood pressure. Inulin clearance [1] 118.6 cc/min. Hippuran clearance [1] 495 cc/min. The renal function tests were consequently normal. Her gene for diabetes insipidus is the only available explanation of the deficient powers of concentration.

It is interesting to compare the objective investigation results with the anamnestic results; this has been done in table 18. It is seen that, in 2 cases, normal powers of concentration

[1] These investigations have been kindly carried out by Dr. O. Hogeman. Normal values: Inulin clearance about 120 cc/min.
Hippuran clearance about 400—420 cc/min.

Table 18.

Comparison between concentration power and anamnestic symptoms in conductors.

Conductor	Number of pregnancies	Highest spec. gravity	Striking thirst	Nightly water consumption
J: IV: 6	1	1.014	—	—
C: VII: 4	5	1.015	+	+
C: VIII: 8	1	1.018	+	—
B: VI: 31	5	1.019	+	—
J: IV: 10	0	1.019	—	—
H: II: 5	2	1.023	+	+
F: VII: 1	0	1.024	—	—
G: VIII: 61	0	1.028	+	+
G: VIII: 60	0	1.029	+	+
B: VIII: 23	0	1.029	—	—
B: VIII: 22	0	1.031	—	—

have been demonstrated in women with anamnestic symptoms. These are 2 sisters, aged 15 and 17 years respectively, whose anamneses may justifiably be described in more detail. The father, who had diabetes insipidus, disappeared from home when the girls were 1 and 3 years old. Since then, the mother has had 2 children by a healthy man, and has therefore been in a particularly good position to make comparisons. The reports on the conspicuous thirst of these girls have been given by themselves and by their mother and maternal grandparents. Since earliest childhood they have been in the habit of drinking during the night, one of them several times, more often than not. They have measured their daily outputs of urine in the home under their mother's control on two consecutive days, the average being 2,550 cc for the elder, and 2,650 cc for the younger (G: VII: 60 and G: VIII: 61).

In 2 other cases in table 18 the discrepancy has the opposite trend. The women concerned here had no striking thirst subjectively, and never drank during the night, but they have plainly lowered powers of concentration. It is particularly strange in the case of J: IV: 6, who did not exceed 1.014, although she had not had subjective symptoms. Both these women had great difficulty in standing the thirst test. One year before the investigation recorded here, J: IV: 10 had been

investigated with a thirst test without previous water loading, and following debarment from water during the previous night: this test was continued to 6.30 p.m. On this occasion she did not exceed 1.018 in specific gravity. The author has tried to test J: IV: 6 again, also, but was not successful.

Another circumstance can be gathered from table 18. The 4 patients with the strongest powers of concentration are all childless (the converse does not hold, however, in that the childless girl J: IV: 10 belongs to the group of those with inadequate concentration). A later chapter will take up the question of the patho-physiology of diabetes insipidus gravidarum and, in connection with that, the possibility that it is not by chance that it is precisely 4 virginal conductors who concentrate normally.

Discussion.

Thus, the investigations, of the conductors have shown that, in certain cases, these subjects behave like normal individuals, pass normal quantities of urine and have normal powers of concentrating their urine. On the other hand, there are also conductors with increased water requirements according to the anamnesis, with plain polyuria and deficient powers of concentrating urine, without its being possible to give this any other cause than the diabetes insipidus gene. Needless to say, it is out of the question to try, on the basis of this small material, to reach any idea of the frequency for this different categories.

In the heterozygotes for the sex-linked diabetes insipidus, then, the gene for the disorder is either purely recessive or else of little effect. In this respect these conductors are analogous with the conductors for a number of other disorders inherited via the sex chromosome. In haemophilia, a number of the heterozygotes are entirely normal, whereas others have slight or plain clinical symptoms and some prolongation of the coagulation time (Schloessmann 1924, Löfgren 1937, Andreassen 1943, Sköld 1944). Waaler (1927) and Wieland (1933) have demonstrated slight defects of the colour sense in a number of conductors for colour blindness of different types, whereas others had a normal colour sense.

There is another way in which the intermediary gene effect may reveal itself in the conductors for diabetes insipidus, and this is by the appearance of severe symptoms during the latter part of pregnancy, in particular, probably, when the woman has been with child more than once.

The occurrence of the slightly or possibly affected heterozygote women makes it very difficult to set a clear-cut boundary between the state of diabetes insipidus and normal water metabolism, and the diagnosis of border cases is very often a matter of opinion. That a normal thirst test did not rule out the diagnosis was already known earlier on. New examples of the limited value of a normal thirst test are provided by cases such as G: VIII: 60 and G: VIII: 61, who despite convincing anamnesis and despite measured polyuria have normal powers of concentration.

CHAPTER 7.

Pedigrees with autosomal genes.

Genetic viewpoints.

Pedigree K.

The mere presence of relatively severely affected women distinguishes this pedigree from those described in the previous sections. The old woman K: II: 2 has had an anamnesis of diabetes insipidus since childhood. Otherwise, the fact that she now shows distinct symptoms might be ascribed to her various pregnancies. The girl K: V: 7, who is no more than a year old, already has plain symptoms. However, some diabetes insipidus symptoms are also found among the female conductors in the sex-linked pedigrees, and though they may seem stronger in these two K women, it is only a difference of degree.

This pedigree is of a different nature from the others in another way also, however. At one place the gene has passed from father (K: III: 9) to son (K: IV: 21), hereby ruling out sex-linked inheritance. An autosomal gene must be in question. The pedigree also shows 2 phenotypically healthy gene-bearing males (K: III: 8 and K: III: 9). It stands to reason that these must be heterozygotes, and as heterozygotism in males is impossible for a gene in the sex chromosome, we have here another indication that the gene in this case is autosomal.

The passage from father to son might theoretically be explained by the transference of the gene through crossing-over from the x- to the y-chromosome. The occurrence of relatively many affected women in the pedigree makes this possibility extremely improbable, however; one is then forced to assume crossing-over in both directions in a number of places in the pedigree.

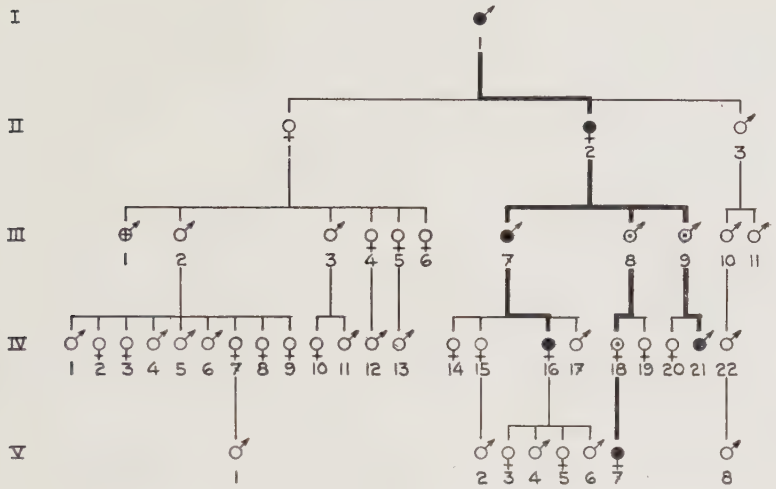


Fig. 27. Pedigree K.

If, then, the gene is autosomal, we must now decide whether it is dominant or recessive. As far as is known, there is no intermarriage in the pedigree, and a gene is concerned which is very rare in the population. The occurrence of 6 affected members in 5 consecutive generations is then incompatible with the assumption of a recessive gene — needless to say, all these 6 cannot be homozygotes. Nor can there be question of an extremely labile mutation, whereby the phenotypically healthy could be regarded as free from the gene, and their affected offspring as new mutations. A mutation lability of this kind must lead to a higher frequency of gene-bearers in the population. Moreover, the otherwise phenotypically healthy women disclose their character of heterozygotes by having the phenomenon diabetes insipidus gravidarum. The gene must be considered dominant, and one is here up against an irregularity in the dominance or — to use the term most commonly used nowadays — incomplete penetrance, such as has already been observed in diabetes insipidus (Alfred Weil 1905, Steiner 1939, Koga 1914, Kurose 1928, Hitomi and Sato 1928 — the last three quoted from Hanhart 1940).

The term penetrance should be taken as purely descriptive, and tells us nothing as to why the disease does not always

manifest itself in a gene-bearer. The cause may be contingent on environment, and the influence of environment may make itself felt even at earliest embryonic stages. Examples of cases where the diabetes insipidus gene is manifested only under the influence of environmental factors are those, where heterozygotes have symptoms only in connection with, or after one or more, pregnancies. The cause may also be genetic in several different ways. The manifestation of the disease may depend on the coincidence of several non-allelic genes, i.e. polyhybrid heredity. It is also conceivable that there is a variation in the effect of normal genes. If the affected gene in a heterozygote is combined with a 'strongly normal' gene in the allelomorphic chromosome, the result will be a phenotypically affected individual. We might also remember that, as diabetes insipidus can be inherited via the sex chromosome, this pedigree K may also have normal genes for the regulation of the water metabolism, which are located in the sex chromosome and can be expected to have varyingly strong effect.

Yet another possibility should be discussed. The varying manifestation may be a result of genotypical asymmetry, with the wider implications which Dahlberg (1926 and 1930) has accorded the term, and which includes the possibility that the character may be shifted not only from the right to the left half of the body, but also from the cranial part to the caudal, or from the ventral side to the dorsal. If the character is in its usual place in the cranial end it may bring on a defect in the diencephalo-hypophyseal system and so cause diabetes insipidus. But if it can be displaced to the caudal end, the characteristic effect of the gene cannot be forthcoming, due to the absence in this half of the body of the specific organ. This is a theoretical possibility which appears probable in other genetic connections. As regards diabetes insipidus, it is only one of the possibilities which are collected under the very comprehensive head of penetrance.

Pedigree L.

This pedigree, whose only affected members are a woman and her daughter, is so small that it cannot be assessed with

certainty. Both the women have severe symptoms, and therefore do not behave as the heterozygotes in the sex-linked pedigrees. On this account, and since the autosomal gene is, on the whole, commoner than that of the sex chromosome, an autosomal gene is probably in question here. As far as information has been received, all other relatives are free from diabetes insipidus. If several skipped generations are not to be assumed, the disease seems to have arisen through gene mutation in the affected mother, L: III: 12. However, it is perfectly conceivable that a couple of generations have been skipped: after all, this occurred in pedigree K, for example, between K: II: 2 and K: V: 7.

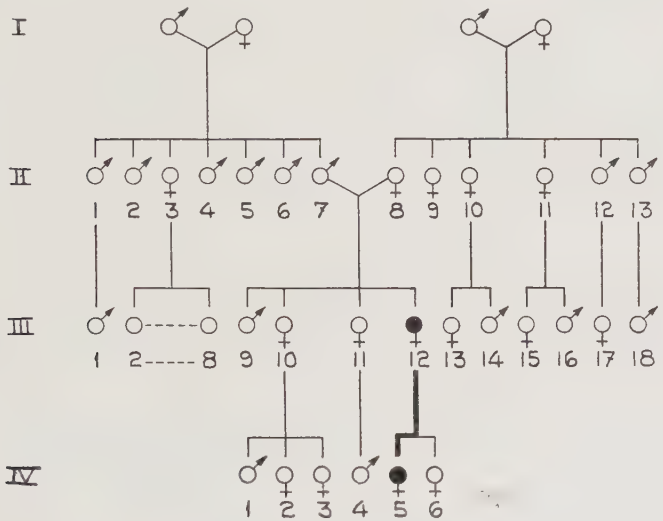


Fig. 28. Pedigree L.

Clinical viewpoints.

Pedigree K.

In all, the material comprises 9 gene-bearers of both sexes, of whom 8 are still living. There are phenotypically affected and healthy gene-bearers of both sexes. Each category is represented by only one or two patients, and it is impossible to give a tabulated survey.

Phenotypically affected members.

Of the affected male gene-bearers, K: I: 1 died a very long time ago, but his abnormal thirst is testifed to by a son and a daughter. The other 2 affected males, K: III: 7 and K: IV: 21, have been clinically investigated. Of the females, K: II: 2 has been investigated in her home at the age of 80 years with a single urine sample, whose specific gravity was 1.006. According to information received, she had the disease even before she became pregnant for the first time. K: V: 7 was not quite a year old when the author visited her, so that there were no prospects for a profitable objective investigation. K: IV: 16 has been marked with the symbol for 'affected' in the pedigree, since on the last occasion of investigation she undeniably showed slight diabetes insipidus, even when not pregnant. However, the choice of symbol here is to a certain extent arbitrary: an investigation 5—6 years earlier would probably have resulted in her being denoted healthy. K: IV: 16 is therefore dealt with in more detail together with the female conductor K: IV: 18.

Time of the onset of the disease.

With the exception of K: IV: 16, the patients in this pedigree, too, had the disease from earliest infancy. In the case of K: V: 7, it is particularly easy to date the first observations of abnormal thirst, since the interview with the mother took place before the girl was a year old. It was in her 6th month of life that she began to cry at night, becoming quiet again only if she was given water to drink.

Case K: IV: 16 shows a later onset for the disease. According to tallying information from the patient herself, her parents, an older sister, and her husband, she did not show the least sign of diabetes insipidus up to the time of her first pregnancy. When pregnant, and particularly during the last months, she developed a diabetes insipidus syndrome which became more intense with each pregnancy, and which was objectively verified in connection with the 4th. The remission was not complete after this 4th pregnancy, and perhaps not after the 3rd, either.

Her present chronic state of slight diabetes insipidus has gradually been acquired in this way.

The intensity of the disease.

One has a general impression that the intensity of the disease is not great in this pedigree, but of course this observation applies only to a small number of cases. The only patient who has been under hospital observation for any length of time is K: III: 7, who was treated for 33 days at the age of 42 years. During this time, the mean daily output of urine was over 2,620 cc. This mode of expression has been chosen since a number of the daily outputs entered in the records are obviously incomplete, though this has not been noted in the customary way. Amounts of 600 cc appear without a plus sign. If the mean is calculated for the 10 first days in hospital, during which time the patient was in bed, it gives the figure of 3,810 cc, which in all probability is more correct than the one above. The largest measured amount of urine was 4,500 cc. This daily output indicates a mild form of the disease, and the figures for the specific gravity point in the same direction; in thirst test the highest figure was 1.018, and in water and thirst test 1.017. A daily output of 2,500 cc was measured during a short stay in hospital in 1944, when the patient was 51 years of age.

K: IV: 21 was under observation in hospital at the age of 15 years. The only measured daily output of urine amounted to 3.320 cc; this figure may be unusually low, however, due to thirst test. During a fairly lengthy thirst test a specific gravity of 1.013 was reached. There are no other observations as to the intensity of the disease in this permanently affected subject.

It would be interesting to compare, within the family, the intensity in the permanent diabetes insipidus with the intensity of the form appearing during pregnancy; nor is such a comparison impossible. While in the Obstetric Clinic a week before her 4th delivery, K: IV: 16 had a highest measured daily output of 6,800 cc, and the mean for 7 days was 5,750 cc a figure which should probably be regarded as a minimum.

In thirst tests during pregnancy she did not exceed a specific gravity of 1.007. Thus, when pregnant, this woman showed a greater intensity for her diabetes insipidus syndrome than her father habitually showed at the age of 42 years.

This circumstance might be considered indirectly to confirm the statement of the conductors in the sex-linked pedigrees who say that, when pregnant, they become as severely affected as the affected male members of the family. An analogy of this kind is not justified, however. In the pedigree K one is comparing two heterozygote gene-bearers with one another. In the sex-linked pedigrees, on the other hand, only the women are heterozygotes, and the men do not have the balancing normal gene. Moreover, it is, of course, in any case impossible to draw any definitive conclusions from one hereditary form to another.

Variations due to age.

As regards the 80-year-old woman K: II: 2, the anamnesis has shown a distinct mitigation of symptoms in old age. For the rest, no variations due to age have been registered by the affected subjects themselves. No objective investigation results concerning this tendency are available within the pedigree.

Fever.

The members of the family have themselves never observed any change in the intensity of the disease in association with fever. There have been no possibilities of objective studies.

Posterior lobe extract.

Only 2 members of the pedigree have been tested with posterior lobe extract, namely K: III: 7 and K: IV: 16. The results of the test on K: III: 7 are shown in fig. 29. (Here the procedure differed somewhat from that used on the male patients in the families A—J. As the intensity of the disease was so low, there was a risk that the diuresis might cease during the thirst test, and the patient was therefore allowed a drink of water every half-an-hour, corresponding to the amount of urine passed every 30 minutes. Nonetheless, the

urine portions on the 2nd test day were so small that the specific gravity and the chloride concentration were determined on 2 portions made into one, thus representing 60 minutes.

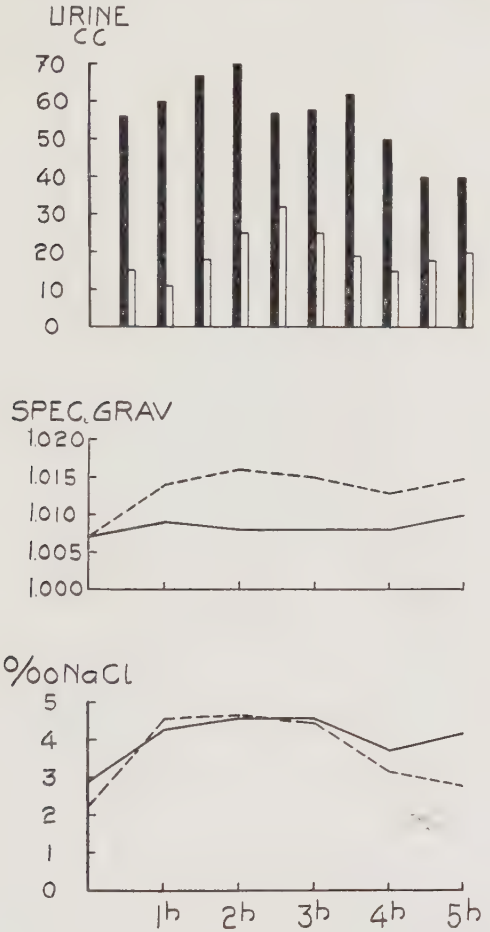


Fig. 29. K: III: 7. Series of urine samples without and with pituitrin. Water is given every half-an-hour to the same volume as the amount of urine passed the foregoing 30 min. period. Specific gravity and NaCl concentration determined only in one-hour-portions. Plain effect from pituitrin seen in volumes and specific gravities.

To obtain comparable data, the values of the 1st test day have also been re-calculated in 60 minute portions). The reduced quantities of urine and the raised specific gravity point to an

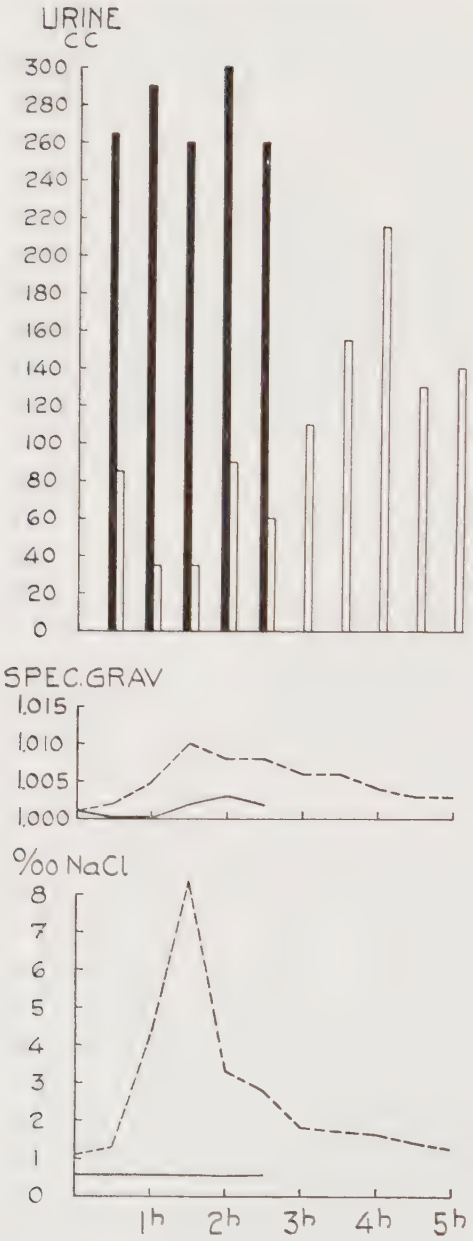


Fig. 30. L: III: 12. Thirst tests without and with pituitrin. Strong reaction of typical kind.

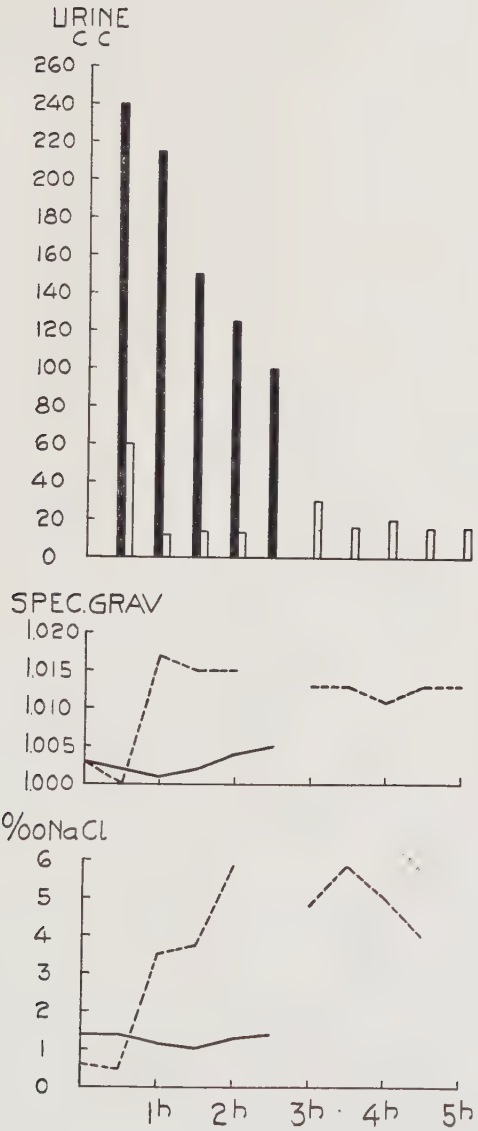


Fig. 31. L: IV: 5. Thirst tests without and with pituitrin. Strong reaction of typical kind.

effect from the hormone. The author cannot explain why the NaCl content did not rise.

In the puerperium following her 4th pregnancy, K: IV: 16 received a test dose of 1 ml Hypadrin. The intention was to make parallel thirst test experiments, such as those used earlier. However, after the Hypadrin dose the diuresis ceased for $2\,^1/_2$ hours. Her thirst disappeared for the entire day. No diagram can be made, but the effect of the extract is indisputable.

The two experiments made have thus indicated that the patients in the pedigree K are susceptible to posterior lobe extract.

Phenotypically normal gene-bearers.

The pedigree contains 2 male conductors and 1 female conductor. One woman, the K: IV: 16 already mentioned several times, was phenotypically healthy while growing up — that is to say, a conductor — but acquired persistent symptoms later, through repeated pregnancies.

Of the male conductors, one — i.e. K: III: 9 — has been under observation in hospital. Here his water and thirst test was quite normal, with a highest specific gravity of 1.028. To the author's knowledge, this is the only published case of a male conductor of diabetes insipidus who has been investigated for powers of concentration; a reservation must, however, be made for the Japanese works, which have not been accessible in the original.

The other male conductor, K: III: 8, has not been under observation in hospital. A sample of morning urine had the specific gravity of 1.020.

K: IV: 16, who according to convincing anamnestic data before her pregnancies had been free from symptoms, is the author's only objectively verified case of diabetes insipidus gravidarum. In the Case Histories, a full description is given of the grounds on which there is reason to assume she had this phenomenon in a strength increasing with each pregnancy. Just before her first delivery the highest daily output measured

was 4,000 cc, and the mean for 7 days was over 2,370 cc (several measurements incomplete). There are no objective results from the 2nd and 3rd pregnancies. Towards the end of the 4th pregnancy, the largest daily output measured was 6,800 cc, and the mean for 7 days was 5,750 cc (probably a minimum). In the water and thirst test during the 4th pregnancy she did not exceed a specific gravity of 1.007. Certain diabetes insipidus symptoms probably persisted even after the 3rd pregnancy, and in any case after the 4th, although there was a distinct mitigation a short time after delivery. Nowadays she drinks 6—8 glasses of water during the day, and 1—2 glasses in the middle of the night. She urinates once a night. In a water and thirst test 10 months after her 4th delivery, she reached the specific gravity of 1.015. It is true that the thirst test performed during her pregnancy could not be completed over the night, as delivery commenced. But when the test was subsequently repeated, the figure of 1.015 had already been reached at the point when the first test had been interrupted.

The female conductor K: IV: 18 was under clinical observation after her 1st pregnancy. Towards the end of this pregnancy she had, according to detailed data from herself and her relatives, an extreme thirst with a water consumption of 5—6 litres per day, and 1 litre per night. This abnormal thirst ceased no later than labour, and after partus she returned to a fully normal water consumption. On investigation 1 year after partus, she had a completely normal water and thirst test, with a highest specific gravity of 1.031. It is important that this woman should be followed up in the future, being objectively studied during any further pregnancies and in the intervals between them. It is to be expected that, as in the case of her cousin K: IV: 16, repeated pregnancies will finally end in her acquiring a permanent diabetes insipidus.

Pedigree L.

Both the affected members of this pedigree, a mother and her daughter, have been clinically investigated.

According to the anamneses, they both had their symptoms before they could speak. They have diabetes insipidus in a relatively intense form. At the time of the investigation L: III: 12 was 28 years old. The largest measured daily output of urine was 11,600 cc, and the mean for 2 days was 9,850 cc. During a thirst test the specific gravity did not exceed 1.003. The symptoms became considerably more severe during pregnancy, when daily outputs of up to 20 litres have been registered in hospital. The patient reports that the symptoms were strongest in the 4th month of pregnancy, possibly indicating that the disease began getting worse at this juncture.

The daughter L: IV: 5, who was 6 years old and weighed 29 kg at the time of the investigation, had a highest measured daily output of 4,450 cc. The mean for 2 days was 4,180. When subjected to a thirst test she did not exceed a specific gravity of 1.005.

The patients themselves have never registered any mitigation of the diabetes insipidus syndrome in connection with fever. Both these patients were remarkably susceptible to posterior lobe extract. See figs. 30 and 31.

CHAPTER 8.

State of health in general. Complications.

The general somatic investigation of the diabetes insipidus patients has not revealed regular disturbances beyond the diabetes insipidus syndrome. Apart from J: V: 3 — a child with very arrested development — none of them presented constitutional dysplasia, e.g. obesity or derangements in the sexual development. There have been no anomalies as regards moisture of the skin, and no tendency to lowered secretion of sweat. The nervous system was also normal.

Table 19.

Number of subjects examined with certain routine methods.

	Ophthalmological examination	*Roentgen of skull*	*Wassermann reaction*
Group AH			
Males	9	8	8
Conductors	6	5	6
Group J			
Males	3	4	2
Conductors	1	1	1
Group K	2	2	2
„ L	2	2	—

Table 19 outlines a number of special investigations which are part of the routine when exploring diabetes insipidus. Eye investigation implies examination at the Ophthalmic Clinic of the Academic Hospital for sight, eyegrounds and visual field. All those investigated were normal in these respects (apart from isolated cases of obviously incidental deviations).

The roentgen examination of the cranium including the sella turcica revealed normal conditions.

The Wassermann reaction was negative, with no exceptions. There is, of course, no reason to expect it to be anything else, but a positive reaction might have called into question the hereditary genesis.

Disturbance in development.

In one single case, J: V: 3, a diabetes insipidus patient showed a severe trophic disturbance. At the age of 2 years 4 months, his body weight was 7.200 gm and his height 75 cm. He could not walk or talk. It is not possible to work out what connection this extreme backwardness may have with the diabetes insipidus syndrome. It is not so very uncommon for those contracting acquired diabetes insipidus at an early date to be under-developed (Gayler 1921, and others). On the other hand, hereditary diabetes insipidus does not usually affect development in this way. In this solitary case, therefore, we are probably up against a chance coincidence with another hereditary or non-hereditary disease.

Diabetes mellitus.

The literature has now and then taken up the question of a causal connection between diabetes insipidus and diabetes mellitus. Hitherto, however, it is only in non-hereditary cases that these complaints have been observed concurrently in the same patient. In acquired diabetes insipidus it is by no means inconceivable that both metabolic derangements may be induced by a common cause. Among 100 cases of diabetes insipidus from the Mayo Clinic, Allan and Rowntree (1931) found only 2 which were complicated with diabetes mellitus: in addition, there was 1 case of glycosuria. So low a frequency makes it likely that the coincidence is due to chance.

In the author's material, 2 cases are complicated with diabetes mellitus, namely B: VI: 34 and J: III: 9. Raised blood sugar values and, in the latter case, a pathological glucose loading curve, show that more than renal glycosuria is in question here. In both cases the patients fell ill about the age

of 50 years. They had no acidosis, and could be regulated without insulin.

A coincidence of this kind has not previously been observed in hereditary cases of diabetes insipidus. There is nothing to suggest that the author's cases are not the result of chance. Apart from the 2 above-mentioned cases of diabetes mellitus, none of the author's patients had sugar in the urine. The fasting blood sugar value was taken on most of them, but was never abnormal. Sugar loading was performed on a small number of the patients, with normal results.

A possible genetic connection between these two diseases has also been sought in the occurrence or diabetes insipidus and diabetes mellitus in the same families. Steiner (1939) noted several cases of the former disease in family investigations based on probands with diabetes insipidus. However, he makes no attempt to test whether the number of diabetes mellitus cases is larger than a correspondingly large material, selected at random, can be expected to contain.

The present author, too, has met with a number of cases of diabetes mellitus among the relations of the diabetes insipidus patients. And, indeed, what else would one expect in a material of this size? In view of the necessary limitation of the work, there has been no systematic collection of reports as to diabetes mellitus, so that any statistical treatment is impossible. The author does not, therefore, submit the cases of diabetes mellitus encountered among the relations; the number was in any case not sensationally large.

Psychic derangements.

Psychic derangements in the form of defects of intelligence have been described in patients with hereditary diabetes insipidus by McIlraith (1892) and Ehrmann (1911). Table 20 shows the cases of constitutional mental derangement found in the author's material among the diabetes insipidus patients. Only those are included who were personally investigated or who carried hospital records. The level of intelligence was determined without psychometric investigation on the impression received by the author when recording the anamnesis,

and otherwise during conversation on school achievements, etc. Defects of intelligence have been positively or negatively assessed on hospital records in 3 patients only, the information thus provided being reliable.

Table 20.

Mental defects in d.i.-patients, examined by the author or otherwise clinically investigated.

Group	Number of affected	Oligophrenics	Psychopathics
AH	13	C: VIII: 7	G: VII: 94 H: III: 4
J	5	J: III: 1 J: III: 5 J: III: 9? J: IV: 8 J: V: 3	
K	5	K: III: 7 K: IV: 21	

The table shows that most of the patients in the group AH were normally developed mentally. There is no reason to assume genotypical connection between the cited forms of psychic constitutional defects, and nothing suggests that the few defects in this pedigree have not been combined with diabetes insipidus by chance.

In the pedigree J all the diabetes insipidus patients are more or less extremely backward. J: III: 9 has been marked with a question mark because, at the investigation, he also presented the picture of paranoid schizophrenia, which makes it more difficult to appraise his prepsychotic state. He, too, was probably primarily feeble-minded. In the pedigree K, 2 of 5 manifestly affected with diabetes insipidus are also mentally backward, i.e. the 2 living males. Without having systematically explored these families with regard to oligophrenia, the author can nevertheless say that, in the families J and K, cases of mental deficiency were common even among those members who did not have diabetes insipidus. Consequently, the material does not warrant any definite pronouncements as to whether we are here dealing with a causal connection or a chance coincidence.

CHAPTER 9.

Prognosis.

It has often been pointed out in the literature that the prognosis *quoad vitam* for hereditary diabetes insipidus is, or may be, markedly favourable; the cases from the Weil pedigree who lived to a very ripe old age are habitually quoted. The author's material provides no reasons for any great revision of this view. The following possibilities should nevertheless be mentioned. 1) The diabetes insipidus syndrome may be thought to be indifferent as regards its effect on length of life. 2) Diabetes insipidus may be expected to have a detrimental effect on the length of life, in several ways. It is possible that the great need of liquid may cause disturbances in feeding during infancy, and it seems likely that those diseases of childhood whose actual danger lies in the risk of drying up would be particularly critical for these children, especially if the diabetes insipidus diagnosis is overlooked. Naturally, when assessing the prognosis of the disease, one does not take these risks into account merely by pointing to a number of patients who have become very old. Finally, it is possible that diabetes insipidus may have detrimental effects even in adults, e.g. on the circulatory system; but there is no concrete support for this. 3) It is conceivable that diabetes insipidus may promote length of life. These patients probably run less risk of concrement in the urinary tract and the complications attendant thereon. In the event of heart trouble, their diabetes insipidus should be adapted to counteract edema, and this must improve the prognosis of the heart disease. Indeed, it is very seldom that one hears of edema in diabetes insipidus

patients, even with heart trouble. It is from the point of view of this argument that the author has, in the Case Histories, given a positive or a negative report as to the presence of edema.

CHAPTER 10.

Diabetes insipidus gravidarum.

The question of the patho-anatomy behind the phenomenon of diabetes insipidus gravidarum has received rather meagre treatment in earlier literature. Its probable connection with the pregnancy changes of the anterior pituitary lobe has been touched on by several authors (Momigliano 1929, Anselmino and Hoffman 1930, Příbrský 1934, Mondt 1941 and Vignocchi 1941). The striking parallelism between pregnancy changes in the hypophysis and pregnancy polyuria has hardly received its due emphasis, however.

It is true both of the morphological changes of the anterior lobe (the presentation here follows Erdheim and Stumme 1909, and Romeis 1940) and of the different forms of pregnancy polyuria as presented in the literature and as they have appeared in the material of the present author, that they become plain in about the 4th—5th month. They increase in intensity, and reach their maximum about the 7th month. After childbirth both phenomena undergo a rapid regression, already manifest within a few days. Considerable variations in the rapidity of the regression have nevertheless been shown both for polyuria and for pituitary changes. It is also characteristic of both these phenomena that they set in earlier and with greater intensity for each new pregnancy (Janzen 1899; author's cases H: II: 2 and K: IV: 16). Diabetes insipidus gravidarum not infrequently appears or is observed for the first time during the 2nd, 3rd or 4th pregnancy. Once the phenomenon has occurred, however, it reappears with very few exceptions in subsequent pregnancies. The involution between the pregnancies

of the morphological changes is not complete; a certain surplus remains after each pregnancy, at any rate for some years. In the same way, one or more bouts of pregnancy diabetes insipidus is seen to be followed by a persistent increase of the diuresis (Wolff 1903; author's cases H: II: 2 and K: IV: 16).

Actually, it is not often one sees so striking an agreement in rhythm between clinical symptoms and morphological changes. It therefore seems very likely that a correlation is in question here, but it is difficult to say what sort. The pituitary changes and the polyuria may be parallel secondary phenomena. All the same, it seems as though the polyuria could be attributed to an increase of those diuretic forces associated in some way with the anterior lobe. Nowadays, it is assumed that the foetus and the placenta form the substances which cause the pregnancy changes of the hypophysis (Romeis 1940).

Thus, diabetes insipidus gravidarum and the enhancement during pregnancy of pre-existing diabetes insipidus must be regarded as phenomena analogous to the slight pregnancy polyuria occurring in a number of healthy women. The more intense symptoms appear in those women whose antidiuretic regulation has been injured by different causes. The heterozygote women can be calculated to have a genotypically conditioned injury of this kind, which is manifest only, or with particular strength, in connection with increased diuretic pressure from the anterior lobe system.

Of the conductors for sex-linked diabetes insipidus investigated by the author, those to reach the highest figures for specific gravity were 4 girls between the ages of 14 and 20 years, who had not as yet had children. Of the 6 mothers (one or more pregnancies) from the same category, only one had normal powers of concentration, namely H: II: 5, who reached the figure 1.024. (A heterozygote from the pedigree K, who had been pregnant once and had then had pronounced diabetes insipidus gravidarum, concentrated to the specific gravity of 1.034.) It may be no mere chance that the virgin conductors concentrate normally to a greater extent, while the mothers more often show insufficient powers of concentration. If a causal connection of this kind is present, it would tally

well with the above view of the connection between the anterior pituitary lobe, pregnancy and water metabolism. To test the tenability of this hypothesis, it is important that the conductors observed while still young, should be investigated several times after they have been through one or more pregnancies.

If the mechanism for diabetes insipidus gravidarum is the one assumed here, it is obvious that it is of no consequence to the symptoms of the mother whether the foetus has diabetes insipidus or not (in connection with Gänsslen's and Fritz's case 1924, several authors have advanced the idea of an influence from the foetus). Chance, however, may make it look as though the existence of the disease in the foetus is decisive. That is to say, if a son with diabetes insipidus is born third or fourth in the family, and the older sibs are healthy, it may easily happen that this very pregnancy of the conductor mother's will see the appearance of pregnancy polyuria for the first time, or with a hitherto unknown intensity. Such cases occur in the author's material (G: VI: 31 and H: III: 4). Needless to say, it might equally well have happened that the affected son was the first-born, and the pregnancy symptoms of the mother appeared in connection with a healthy child, born later.

Summary.

After describing the literature on the patho-physiology of the diabetes insipidus syndrome, the author surveys earlier works on hereditary diabetes insipidus. It appears from this that it has not previously been possible to demonstrate the occurrence of sex-linked heredity, although a few pedigrees, previously communicated, by several authors are considered to uphold the possibility of a sex-linked gene for the disorder.

The author's material contains 5 pedigrees, with a total of 83 gene-bearers, known from personal investigation, hospital records, or the evidence of relatives. 40 of these 83 gene-bearers have been denoted as manifestly affected, and 43 as conductors; the dividing-line between the 2 categories is not always sharp, however. 36 gene-bearers have been investigated in hospital; a further 17 have been investigated with a direct anamnesis. The genealogical investigation covers about 5.500 persons in all.

Results:

1. Previous compilations of hereditary diabetes insipidus have shown a statistically significant or probable preponderance of males among the affected. The author shows that if the material is selected in a way to eliminate sex-linked genes, the men stand to the women in the ratio 1:1 (Cf. p. 30).

2. The mere preponderance of males in older material makes probable the existence of an x-chromosome-linked gene for diabetes insipidus in certain families. This is now confirmed by 3 of the author's pedigrees, which answer all requirements for sex-linked heredity. In all, 32 affected males and 40 female conductors are known in these pedigrees. One of the pedigrees is large, containing 7 families which go back

to a common female ancestor; it has thus been possible to follow the gene through 9 generations in a manner fully conformable with sex-linked heredity.

3. The author's remaining 2 pedigrees contain 9 and 2 gene-bearers respectively. In the larger pedigree, the disorder is unquestionably due to an autosomal gene, and this is probably true of the smaller one also. The occurrence of symptom-free male and female gene-bearers shows an irregularity in the so-called penetrance. A male heterozygote for the autosomal gene has proved, on clinical examination, to have fully normal powers of concentration: this is of interest since, according to the literature at the author's disposal, careful investigation of such symptom-free heterozygotes does not seem to have been carried out earlier.

4. The clinical investigation of the manifestly affected has in most respects tallied with previous observations. One or two cases have yielded objective confirmation of the disease's known tendency of becoming less intense with advancing age. Yet more interesting is the fact that the affected males from the sex-linked pedigrees fall into two groups, differing in an important respect. 9 investigated patients from 2 of the pedigrees are plainly susceptible to pituitrin, or at any rate never clearly refractory. 2 similarly investigated patients from the 3rd sex-linked pedigree did not react to pituitrin in repeated investigations according to the author's procedure. A 3rd patient in the same pedigree, tested with another technique, is probably also refractory. In view of this difference, and supported by a not very certain difference in the intensity of the disease, there is reason to assume that one of the sex-linked pedigrees goes back to an independent mutation — that is to say, that the sex-linked genes for diabetes insipidus appear in a series of multiple allelism.

5. 24 of the conductors of the sex-linked pedigrees have been investigated anamnestically. Of these, 11 — i.e. $45.8 \pm \pm 10.2$ %, were subjectively free from symptoms, while 13 — or 54.2 ± 10.2 % — showed slight or distinct symptoms, sometimes with nightly consumption of water. In a hospital investigation of 11 conductors, one group has been shown to have

fully normal powers of concentration, while another was shown to have deficient powers, the only available explanation of this being their diabetes insipidus gene. Slight polyuria was objectively established in some of the conductors. (Unquestionable heterozygotes were not made the object of more detailed investigations in hospital at an earlier date, and only in 2 families have rather indeterminate data been elicited, indicating that the disease can manifest itself with faint symptoms in heterozygotes.)

6. According to anamnestic accounts, 9 of the conductors for the sex-linked gene (7 living, 2 now dead) and 2 heterozygotes for the autosomal gene have, in the latter half of their pregnancies, shown plain or severe symptoms of diabetes insipidus, which were allayed within a short period, or disappeared immediately after delivery. In a few cases, the phenomenon has appeared with increased intensity for each fresh pregnancy. On the other hand, some conductors have in all probability shown no such pregnancy symptoms, although repeatedly with child. The phenomenon of diabetes insipidus gravidarum has been observed in a female bearer of the autosomal gene, who was investigated during her 4th pregnancy and 10 months after its termination. According to her anamnesis, this woman was symptom-free when young, but after 4 bouts of diabetes insipidus gravidarum, each one more intense than the last, she has gradually acquired permanent symptoms.

CASE HISTORIES

Pedigree AG.

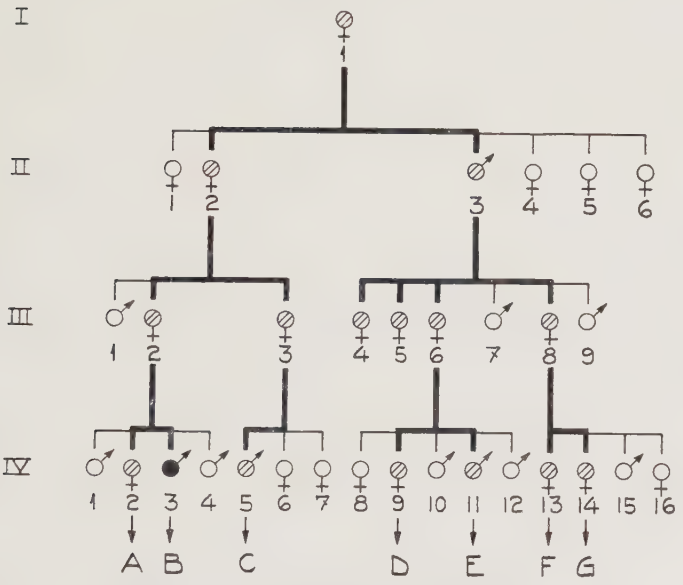


Fig. 32. Pedigree AG, generations I—IV.

I: 1. ♀ b. 1712. First ancestor in this family tree, and presumably a gene-bearer.

II: 1. ♀. 1,063 descendants of this woman have been genealogically traced. No case of d.i. is known among them.

II: 4—II: 6. ♀. The descendants are very imperfectly worked out.

III: 1. ♂. No case known among 192 decendants.

III: 4. ♀. As the daughter of a presumably gene-bearing man, she can be taken to have been a conductor. No known cases among 374 descendants.

III: 5. ♀. Presumably a conductor, on the same grounds. No known cases among 169 descendants.

III: 7 and III: 9. ♂. As sons of a presumed male gene-bearer, they can be assumed free of genes. Descendants not followed up.

IV: 1. ♂. No known cases among 85 descendants.
IV: 2. ♀. See fam. A, fig. 33.
IV: 3. ♂. See fam. B, fig. 34.
IV: 4. ♂. No case of d.i. known among 40 descendants.
IV: 5. ♂. See fam. C, fig. 35.
IV: 6. ♀. No case known among 45 descendants.
IV: 7. ♀. No case known among 101 descendants.
IV: 8. ♀. No case known among 169 descendants.
IV: 9. ♀. See fam. D, fig. 36.
IV: 10. ♂. No case known among 152 descendants.
IV: 11. ♂. See fam. E, fig. 37.
IV: 12. ♂. No case known among 84 descendants.
IV: 13. ♀. See fam. F, fig. 38.
IV: 14. ♀. See fam. G, fig. 39.
IV: 15. ♀. No case known among 47 descendants.
IV: 16. ♀. No case known among 98 descendants.

Family A.

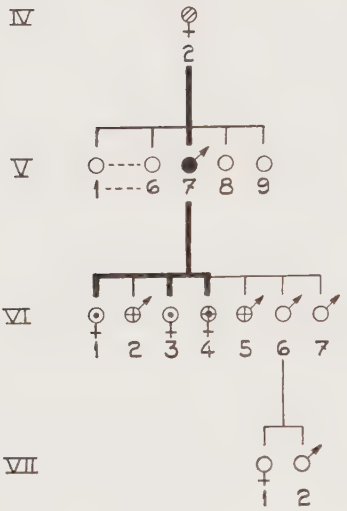


Fig. 33. Family A.

A: IV: 2. ♀ b. 1800 in Hällefors, Örebro län, d. 1868.

Conductor.

The author's informants did not know the patient personally. It is probable she had no symptoms, as though her son, A: V: 7, had told his children that her brother, B: IV: 3, had suffered from the complaint, they had never heard about such symptoms in their paternal grandmother.

A: V: 7. ♂ b. 1841 in Säfsnäs, Kopparbergs län, d. 1919.

D.i. according to evidence received.

The author has met the daughter, A: VI: 1, and the sons A: VI: 6 and A: VI: 7. The father was a so-called water-drinker all his life, and knew it was a hereditary complaint. He could empty a one-litre scoop at a draught. Consumption during the 24 hours: 8—10 litres. Drank several times during the night. His thirst was vividly described in a letter from a nephew. Known to be a water-drinker by several persons in his home tract, whom the author has met.

A: VI: 1. ♀ b. 1867 in Grangärde, Kopparbergs län.

Conductor.

Mother reputed healthy. When visited on May 1943 the patient showed advanced senility. Had never been exceptionally thirsty. Did not drink during the night. Had never been pregnant.

A: VI: 3. ♀ b. 1871 in Grangärde, d. 1940.

Conductor.

According to three sibs she had not shown any symptoms. Had not been pregnant.

A: VI: 7. ♂ b. 1884 in Grangärde.

Polydipsia.

Oligophrenic man, who could not get through school and had always lived at home. Ate voraciously when a child. Had always drunk a great deal. Was considered by a brother and a sister to have 'inherited the thirst disease from Father'. The local schoolmaster also considered him to have the disease. It was, however, generally agreed that he drank less than his father. He often drank during the night, but not regularly. Usually urinated once a night. Able to empty a 1-litre scoop all at once.

Investigated in his home $^{29}/_{5}$ 1943. Debarred from water all night, under control. Morning urine 7 a.m.: Specific gravity: 1.028. No sugar, no albumin. Not particularly thirsty. Continued to thirst spontaneously during work. After a further 1 $^{1}/_{2}$ hours he passed 20 cc urine, specific gravity: 1.029. 9.83 ‰ NaCl.

Interpreted as a case of imitation polydipsia in an imbecile, induced by the d.i. of the father.

A: V: 7 had 8 sibs 6 of whom have offsprings. No further case of d.i. has come to light among 112 descendants of these — children dead in early infancy not included.

Family B.

B: IV: 3. ♂ b. 1803 in Hällefors, Örebro län, d. 1863.

D.i. according to evidence received.

Widely believed in the family to have suffered from the thirst disease. Grandson B: VI: 9 on the male side is a doctor, and considers there to be no doubt of this. He has met the widow of B: IV: 3, and has received definite testimony on the point from his own father. The grandchildren B: VI: 31 and B: VI: 33 both know they heard their mother speak of her father's abnormal thirst. Even the grandchildren of a sister of B: IV: 3 are acquainted with the matter. A: VI: 6 writes as follows: 'Our father told us he had an uncle on his mother's side who was apparently a water-drinker'.

B: V: 5. ♀ b. 1839 in Hällefors, d. 1929.

Conductor.

According to the grandsons on the female side, B: VII: 25 and B: VII: 26, both of whom knew her well, she showed no symptoms. Nothing known of the situation during pregnancy.

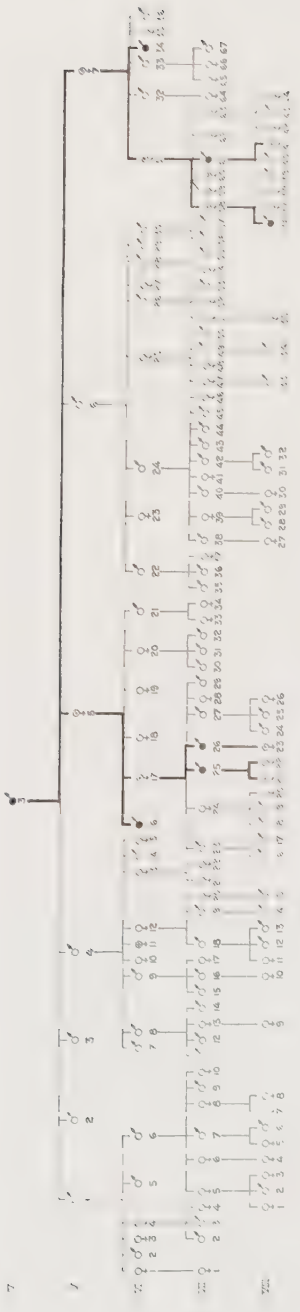


Fig. 34. Family B.

B: V: 7. ♀ b. 1846 in Hällefors, d. 1936.

Conductor.

The author has met the children B: VI: 31 and B: VI: 33. According to them, she had no symptoms either ordinarily or during pregnancy.

B: VI: 16. ♂ b. 1864 in Grythyttan, Örebro län, d. 1916.

D. i. according to evidence received.

Thirst disease in this patient testified to by a number of relations, including the sister B: VI: 17 (by letter), and the nephews B: VII: 25 and B: VII: 26, and cousins B: VI: 31 and B: VI: 33 (by personal communication). The nephew B: VII: 25, who himself suffers from the disease, was employed by the patient for 2 years. They had the complaint to about the same degree. The patient could easily drink 1 litre at a time, and drank during the night. Committed suicide in what, according to the description, was typical melancholia.

B: VI: 17. ♀ b. 1867 in Hällefors, d. 1942.

Conductor.

The sons B: VII: 25 and B: VII: 26 had neither noticed nor heard mention of symptoms in the mother, not even during pregnancy. The author has corresponded with her, and she has not said anything about experiencing abnormal thirst.

B: VI: 31. ♀ b. 1873 in Söderfors, Upsala län.

Clinically investigated conductor.

Father healthy. During childhood and youth she had always been well, on the whole; had had 5 full-term pregnancies and 2 abortions, 1 early

and 1 late. Gall-stone attacks (diagnosis not verified by roentgen) at long intervals for many years. Not aware of having had albumin in the urine. Suffering from shortness of breath for the last 10 years; has been treated for raised blood pressure. Has always been considered to drink more than is normal, above all as a child, though by no means as much as the male members of the family thus afflicted. As a child, she was scolded by her mother for drinking so much. Her thirst was greatly increased during pregnancies: 'then I used to drink something awful!' Also drank during the night at those times. This phenomenon recurred at each pregnancy. Under observation at the Medical Clinic of the Academic Hospital, Upsala, $^{29}/_{1}$—$^{31}/_{1}$ 1941. A 68-year-old pyknomorphic woman, young for her age. Some cyanosis of the lips. Slight ankle edema. Heart normal at physical examination. Blood pressure: 190/100. Ecg.: normal. Nervous system: normal. N.P.N.: 43 mgm%. Creatinine clearance: 69 ml/min. Urine normal. Water and thirst test, see table 21. Maximal specific gravity 1.015.

B: VI: 34. ♂ b. 1878 in Söderfors, d. 1939.

Clinically verified d.i.

Treated at the Medical Clinic of the Academic Hospital:

$^{24}/_{8}$—$^{24}/_{9}$ 1920 on the diagnosis *diabetes insipidus*
$^{21}/_{7}$—$^{13}/_{8}$ 1932 „ „ „ „ „ + *bronchopneumonia.*
$^{2}/_{5}$—$^{21}/_{5}$ 1938 „ „ „ *Vitium organicum cordis (insuff. valv. aortae)* + *angina pectoris.*
$^{14}/_{4}$—$^{15}/_{4}$ 1939 „ „ „ *Cardioarteriosclerosis* + *infarctus cordis.*

Had always drunk a great deal of water as far back as he can remember — according to his mother, since earliest childhood. At the age of 40 years his diuresis for the 24 hours was 13 litres. Had *enuresis nocturna* as a child; subsequently trained himself to wake up to urinate, which was necessary 4—5 times nightly. During influenza in 1918 his temperature was 38—39° C, without any marked change in thirst or quantity of urine.

When investigated in 1920 he was described as of normal constitution and well-covered. No edema. Internal organs normal. Nervous system normal. Blood pressure: 135/65. Fasting blood sugar: 0.120 %. Urine normal. Specific gravity 1.002—1.008. Amount of urine in 24 hours: 4,130—12,380 cc. Mean for 28 days: 7,840 cc. After admission he had a moderate temperature for 3 days; it was during this time that the greatest outputs, *i.e.* of more than 12 litres was measured.

In July 1932 he was admitted for fever following operation for septum deviation. Pneumonic sounds at the base of the right lung.

No edema. Daily output: 2,300—5,700 cc. Mean for 22 days: 4,090 cc. No albumin. Sediment normal. 1 % sugar in the urine on admission. Urine subsequently free from sugar, with specific gravity 1.005—1.007. Blood sugar fasting values slightly raised. Maximum: 0.168 %.

In 1938 an aorta insufficiency was diagnosed. Blood pressure: 180/90. Diastolic murmur over the sternum. No dyspnoea in repose, no cyanosis, no edema. Daily output of urine: 1,700—3,450 cc. Mean for 14 days: 2,520 cc. Slight glycosuria alternating with sugar-free urine. No albumin. Sediment normal. Specific gravity 1.009—1.015 for sugar-free urine. Fasting blood sugar: 0.150—0.200 %.

Investigation at an ambulant call on $^{15}/_{2}$ 1939 revealed no edema. Admitted to hospital $^{14}/_{4}$ 1939 for cardial infarct. No edema. Died within 24 hours. Pathological diagnosis: *Cardioarteriosclerosis gravis + Myocarditis chronica fibrosa + Hypertrophia et dilatatio cordis + Arteriosclerosis aortae + Stasis acuta organorum + Oedema pulmonum.* The central nervous system was not examined.

B: VII: 25. ♂ b. 1893 in Grythyttan, d. 1943.

Clinically verified d.i.

Father healthy. According to a letter from his mother in 1941, the son had shown abnormal thirst from at least the age of 3 years. Has drunk a great deal of water as far back as he himself can remember. The symptoms were most marked round the age of 20 years, when he consumed 10—15 litres per 24 hours. Woke up several times each night. After the age of 30 years the symptoms slowly became less intense. 1943 he estimated his daily output of urine at 4—5 litres. Drank once to twice during the night. When he was younger he could drink 1—1 $^{1}/_{2}$ litres at a time, but could not take such large quantities the last years of life.

Was very fat from about the age of 30 years. From the age of 45 years has suffered from severe bronchial asthma, losing much weight. Treated at the Medical Clinic of the Serafimer Hospital, Stockholm,[1] $^{18}/_{5}$—$^{7}/_{6}$ 1939 on the diagnosis: *Diabetes insipidus + Cardiosclerosis cum angina pectoris.* Weight: 106 kg. Daily output of urine: 2,900—6,100 cc.; mean for 19 days: 4,370 cc. Specific gravity 1.001—1.014. Under observation at the Medical Clinic of the Academic Hospital $^{18}/_{8}$—$^{30}/_{8}$ 1943. Lean pyknic without dysplasia. General condition affected, with marked cyanosis and chronic moderate asthma. No edema. Weight: 72 kg. Blood pressure 165/140. Ecg.: Signs of coronary sclerosis. N.P.N.: 46 mgm%. Urine normal. Daily output: 3,030—4,500 cc; mean for 8 days: 4,100 cc. Specific gravity: 1.004—0.011. Reacts to pituitrin, see diagram fig. 12.

[1] The record citied by kind permission of the head of the clinic, Professor A. Kristenson.

B: VII: 26. ♂ b. 1895 in Grythyttan.

Clinically verified d.i.

Same information from the mother as for B: VII: 25. Has had thirst disease as long as he himself can remember. At the age of 20 years, he says, he drank about 15 litres per 24 hours, and could pass 2—3 litres of urine at one time. Nowadays he drinks 8—10 litres daily. Urinates every other hour. Drinks and urinates about 3 times a night. No decrease of thirst during a fever (*angina tonsillaris*). Has otherwise been healthy, on the whole. Under observation at the Medical Clinic of the Academic Hospital $^{12}/_{10}$—$^{16}/_{10}$ 1943. Large pyknic without dysplasia. General condition good. No edema. Apart from hypertonia (blood pressure: 200/125) and slight myocardiac changes in the ecg., the internal organs and nervous system showed no morbid signs. N.P.N.: 33 mgm%. Urine normal. Daily output: 9,870 and 7,000 cc. Specific gravity: 1.002—1.015. Reacts to pituitrin, see diagram fig. 13.

B: VII: 58. ♀ b. 1894 in Söderfors.

Conductor.

Father healthy. In a personal interview she stated that she was not thirstier than normal individuals. Never drinks during the night. None of her 3 pregnancies was accompanied by any marked increase of thirst (a relatively trustworthy statement, as her mother had had *d.i. gravidarum*, and brought the subject up during the patient's pregnancies). Treated at the Surgical Clinic of the Academic Hospital $^{13}/_{4}$—$^{29}/_{7}$ 1921 for appendicitis abscess. After the operation, there was a 17 days' period of micturition difficulty, so that the patient was catheterized. The information as to the daily output during this time is therefore reliable: it varied from 1,050—3,200 cc, with an average of 1,940 cc.

Thirst test in her home $^{16}/_{9}$—$^{17}/_{9}$ 1943. It was not made under control, but the patient is an intelligent and conscientious woman, and entered into the investigation with spontaneous interest. Drank nothing from 12 noon on $^{16}/_{9}$ to 12 noon on $^{17}/_{9}$. Only ate dry food. This resulted in a maximal specific gravity of 1.021. Specific gravity of the night urine: 1.009. In September 1944 the total amount of urine passed during two consecutive normal days and nights was 3,400 cc. — *i.e.* an average of 1,700 cc per 24 hours.

B: VII: 61. ♂ b. 1898 in Söderfors.

Clinically verified d.i.

During the first years of life the patient was noticed by his mother to drink a very great deal, and to pass large quantities of urine. He has suffered from severe thirst as long as he him-

self can remember. The disease reached its height round about the age of 20 years, when he himself measured the daily output of urine, and found it to be 8—10 litres. Noticed a distinct regression subsequently. At present urinates and drinks once to 3 times a night. Always been healthy otherwise.

Under observation at the Medical Clinic of the Academic Hospital $^{6}/_{12}$—$^{9}/_{12}$ 1943. Large pyknic. Not dysplastic. No edema. Xanthomas in the medial corners of the eye. No morbid signs from internal organs or nervous system. Blood pressure: 145/90. N.P.N. 35 mgm%. Urine normal. Daily output: 8,750 and 6,500 cc. Specific gravity: 1.003—1.008. Reacts to pituitrin, see diagram fig. 14.

B: VIII: 21. ♀ b. 1920 in Karlstad, Värmlands län.

Conductor.

Mother healthy. On her own and her father's showing, the patient has not differed in her water requirements from her clinically investigated sister. Has not been pregnant.

B: VIII: 22. ♀ b. 1923 in Karlstad.

Clinically investigated conductor.

Has always been healthy on the whole. Does not drink more than the average person. Never drinks during the night. Has never had albumin in the urine or other signs of kidney trouble. Has not been pregnant. Under observation at the Medical Clinic of the Academic Hospital $^{18}/_{8}$—$^{20}/_{8}$ 1943. Healthy young girl. No dysplasia. No edema. Blood pressure: 125/80. N.P.N.: 35 mgm%. Urine normal. Water and thirst test, see table 22. Maximal specific gravity: 1.031.

B: VIII: 23. ♀ b. 1927 in Botkyrka, Stockholms län.

Clinically investigated conductor.

Mother healthy. Patient has always been healthy on the whole. Never had any symptoms of kidney trouble. Her water needs do not differ in any way from those of her companions. Neither she nor her mother have observed any enhanced thirst.

Under observation at the Medical Clinic of the Academic Hospital $^{18}/_{8}$—$^{20}/_{8}$ 1942. Girl of normal build and healthy appearance. No edema. No morbid symptoms from internal organs or nervous system. Blood pressure: 120/70. N.P.N.: 29 mgm%. Urine normal. Water and thirst test, see table 23. Maximal specific gravity: 1.029.

B: VIII: 36. ♂ b. 1924 in Ludvika, Kopparbergs län.

Clinically verified d.i.

Father healthy. The patient's great desire for water was noticed by the mother in his second week of life, when he used, for example,

to suck saliva from her lips after having been suckled. He himself thinks he has had the same intensity of thirst all his life. At present the consumption of water and amount of urine passed is 10—12 litres per 24 hours. Drinks and urinates once to twice a night.

Under observation at the Medical Clinic of the Academic Hospital $^{6}/_{12}$—$^{10}/_{12}$ 1943. Young man of healthy appearance, and with no anomalies in his habit. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 110/70. N.P.N.: 36 mgm%. Urine normal. Daily output: 8,450, 10,800 and 7,500 cc. Specific gravity: 1.002—1.010. Reacts to pituitrin, see diagram fig. 15.

B: VIII: 41. ♀ b. 1941 in Tierp, Upsala län.

Conductor.

Mother healthy. Patient treated at the Children's Clinic of the Academic Hospital $^{28}/_{9}$ 1942—$^{26}/_{2}$ 1943, and $^{6}/_{12}$ 1943—$^{7}/_{4}$ 1944 on the diagnoses: *Coeliacia* + *Conducens diabetes insipidus hereditarius.* Neither parents nor hospital staff have noticed any striking thirst, except temporarily in connection with diarrhoea. Does not usually drink during the night. Specific gravity $^{9}/_{12}$ 1942: 1.010. Daily output not measured.

Family C.

C: VI: 2. ♂ b. 1852 in Ljusnarsberg, Örebro län, d. 1914.

D.i. according to evidence received.

The author has met the daughter C: VII: 4 and the son C: VII: 7. The father used to drink enormous quantities of water ever since the children can remember, though somewhat less as he got older. He would drink a whole 1-litre scoop at a draught; used to get up at night to drink.

C: VII: 1. ♀ b. 1876 in Ljusnarsberg.

Conductor.

Emigrated to America in 1893. According to her sibs, who have a certain contact with her, she is healthy. Nobody has heard it said that she suffered from abnormal thirst. Has not been pregnant.

C: VII: 4. ♀ b. 1882 in Ljusnarsberg.

Clinically investigated conductor.

Mother healthy. Patient treated for sinusitis, but has otherwise always been healthy. Has not to her knowledge had albumin in the urine or other signs of kidney disease. Has always drunk rather more than people do normally, but less than her father and her son C: VIII: 7. Ever since childhood, she has got up at least once a night to drink. Considerable increase of thirst during the final months of pregnancy.

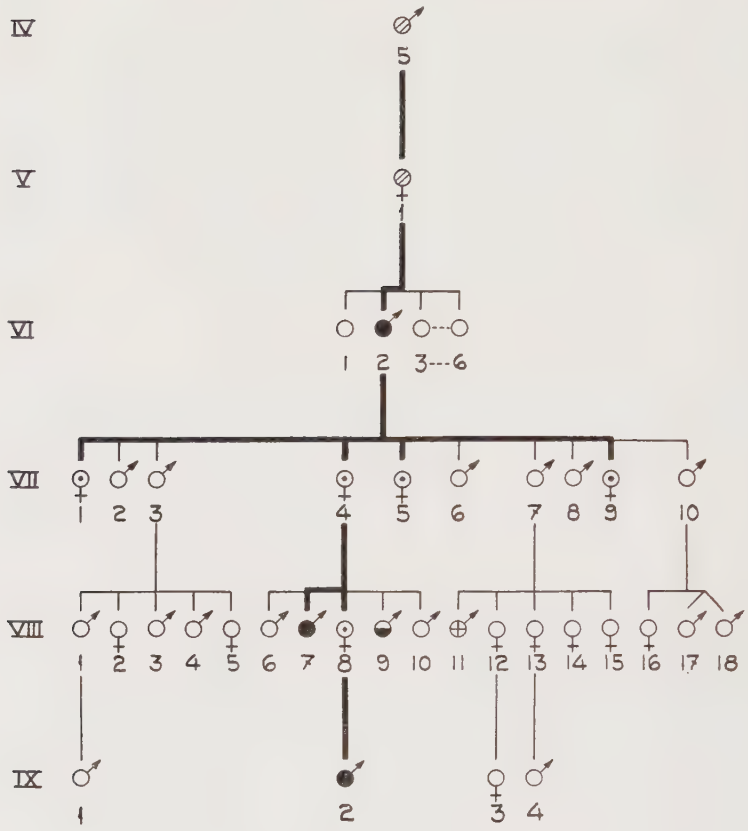


Fig. 35. Family C.

Under observation at the Medical Clinic of the Academic Hospital $^{26}/_{7}$—$^{29}/_{7}$ 1943. Elderly pyknomorphic woman of healthy appearance. without dysplasia. No edema or other signs of incompensation. Blood pressure: 210/115. Otherwise no signs of disease from internal organs or nervous system. Ecg. normal. N.P.N.: 30 mgm%. Creatinine clearance: 88.9 ml/min. Urine normal. Urine output during 24 hours when a thirst test was made without water loading: 2,150 cc. Water and thirst test, see table 24. Maximal specific gravity: 1.015.

C: VII: 5. ♀ b. 1884 in Ljusnarsberg.

Conductor.

Emigrated to America in 1911. According to her sibs, she had no symptoms. She has not been pregnant.

C: VII: 9. ♀ b. 1896 in Ljusnarsberg.

Conductor.

Symptom-free according to her sibs. Has not been pregnant.

C: VIII: 7. ♂ b. 1912 in Ludvika.

Clinically verified d.i. + Oligophrenia.

Father healthy. The patient has suffered from great thirst since childhood — according to the mother 'from the very beginning'. Drinks and urinates 2—3 times a night, sometimes as many as 5 times. Has always been mentally backward; failed to get a remove at school 3 years running, and left before the regular leaving time.

Under observation at the Medical Clinic of the Academic Hospital $^{26}/_{7}$—$^{29}/_{7}$ 1943. General physical condition good. Pyknomorphic without dysplasia. Sullen imbecile not willing to be investigated. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 160/85. N.P.N.: 30 mgm%. Daily output of urine: 4,120 and 3,520 cc. Specific gravity: 1.003—1.004. Reacts to pituitrin, see diagram fig. 16.

C: VIII: 8. ♀ b. 1916 in Ludvika.

Clinically investigated conductor.

Erythema nodosum at the age of 17 years. Otherwise, healthy on the whole. Has never had kidney trouble, as far as she knows.

Does not consider herself to have abnormal water requirements. Her mother considers this child to have drunk decidedly more when young than the two healthy brothers, and considerably less than the two affected ones. Markedly increased thirst during her one pregnancy hitherto, when according to her mother, she drank 'colossally'.

Subsequent to her son's birth she generally drinks once during the night; this she attributes to being waked by her son.

Under observation at the Medical Clinic of the Academic Hospital $^{26}/_{7}$—$^{29}/_{7}$ 1943. A young healthy woman with pyknic proportions. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 140/80. N.P.N.: 27 mgm%. Creatinine clearance: 135 ml/min. Urine normal. Water and thirst test. see table 25. Maximal specific gravity: 1.018.

C: VIII: 9. ♂ b. 1920 in Ludvika.

Clinically observed: Polydipsia? D.i? + Oligophrenia.

According to the mother's anamnesis the patient has drunk a great deal from infancy. 'Always pestered for water as soon as he could make himself understood'. Is nevertheless said to have drunk appreciably less than the brother C: VIII: 7. The patient himself has said that he usually drinks every other hour during the day, then consuming 1—2 litres at a time. There is reason to believe that these data are in large measure boasts. Drinks and urinates once to 3

times a night. He may also sleep right through the night without drinking anything, in which case the urine is fairly dark. Has always been somewhat backward. Unable to keep up with the others at school.

Under observation at the Medical Clinic of the Academic Hospital $^{19}/_{1}$—$^{21}/_{1}$ 1944. Young pyknomorphic man with good general condition. No dysplasia. Gives the impression of moderate debility. Recalcitrant at the investigation. No edema. No signs of disease from internal organs. Blood pressure: 165/90 (patient irritable during the measuring). N.P.N.: 26 mgm%. Urine normal. Daily output: 2,400 cc. Spec. grav. on admission: 1.006. Thirst test $^{20}/_{1}$: Debarment from water under control 8 a.m.—1.30 p.m. Able to yield samples of urine only at the following times during the day:

	Volume	Specific gravity
8 a.m.	675 cc	1.007
9.30 a.m.	460 cc	1.007
3.30 p.m.	320 cc	1.013
8.15 p.m.	380 cc	1.021

Although he had not been debarred from water after 1.30 p.m., he reached the spec. grav. of 1.021.

Pituitrin test with ureter catheter made on the following day. It was intended to make another complete water and thirst test to arrive at a diagnosis. However, the patient left the hospital in a temper, and could not be induced to remain another 24 hours. Epicrisis: The anamnesis is highly suggestive of d.i. As the patient is an oligophrenic and has an older brother with d.i. he could also be subject to imitation polydipsia. The fact that he reaches the specific gravity of 1.021 without any rigid debarment from water must be taken as a strong argument against the diagnosis of d.i. The mother and sister, who are heterozygotes, never reached so high a figure.

C: IX: 2. ♂ b. 1940 in Ludvika.
Clinically verified d.i.

Father healthy. The mother noticed the thirst disease in her son when he was quite an infant. Took him to a doctor for his abnormal thirst, and was advised to ration his supply of water; this proved impracticable, as the child screamed violently and looked ill. At the age of 3 years he woke to drink water and urinate 2—3 times a night, sometimes oftener.

Under observation at the Medical Clinic of the Academic Hospital $^{26}/_{7}$—$^{29}/_{7}$ 1943. Lively, normally developed 3-year-old. Body weight 14.7 kg. No dysplasia. No edema. No signs of disease from internal organs or nervous system. Urine normal. Daily output 1,200 and 1,710 cc. Specific gravity: 1.002—1.010. Pituitrin tests could not be performed, as he could not be got to urinate at regular times.

The 5 sibs of C: VI: 2 were all without offsprings, so far as known.

Family D.

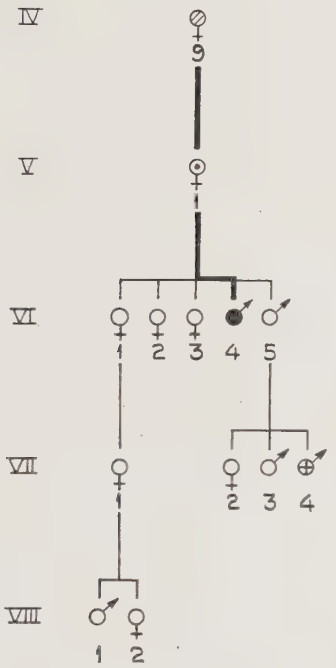


Fig. 36. Family D.

D: V: 1. ♀ b. 1834 in Hällefors, d. 1912.

Conductor.

On the evidence received in 1944 from the daughter D: VI: 3 and the son D: VI: 4 she had no symptoms. Nothing known of the situation during pregnancies.

D: VI: 4. ♂ b. 1874 in Hällefors.

Verified d.i.

Father reputed healthy. The patient was known among a large number of persons in Hällefors — workmates and others — for his great thirst, 'spends most of his time under the pump'. Has drunk a great del as far back as he can remember. Wakes up a couple of times a night to drink. His thirst is less intense now he is older. Urine passed under control: light, clear as water. Specific gravity: 1.006. NaCl.: 3.16 ‰. Urine otherwise normal.

Family E.

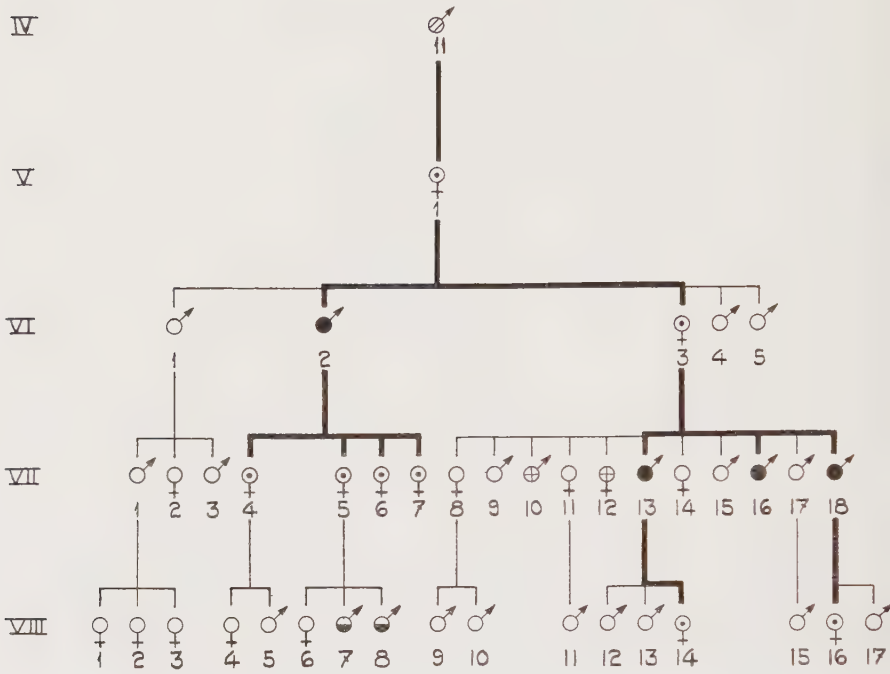


Fig. 37. Family E.

E: V: 1. ♀ b. 1834 in Hällefors, d. 1907.

Conductor.

The author has met her daughter-in-law, and many of her grandchildren. She is reputed to have had no symptoms. Nothing known of the situation during pregnancies.

E: VI: 2. ♂ b. 1858 in Hällefors, d. 1928.

D.i. according to evidence received.

Father reputed healthy. On the evidence of his widow, his daughters and several nephews and nieces, the patient suffered from tremendous thirst all his life. Could drink more than 1 litre at a time. Woke up several times a night to drink and urinate. The last 12 years of his life he had heart trouble, with shortness of breath and blue lips. Suffered from swelling of the legs only a few weeks before he died.

E: VI: 3. ♀ b. 1860 in Hällefors, d. 1943.

Conductor.

According to her eldest daughter, this case suffered from severe

thirst and passed large quantities of urine during pregnancy, when she would drink at night, too, and showed as marked symptoms as those of the sons with thirst disease. The thirst disappeared a short time after each delivery. On account of the large number of children, the daughter had seen the phenomenon repeated several times, and had discussed it with her mother. The son E: VII: 13 also knew about it.

E: VII: 4. ♀ b. 1896 in Närkes Kil, Örebro län.

Conductor.

Interviewed in May 1944. Healthy mother. The patient has always drunk more than is customary, but by no means so as to attract attention. Does not drink at night. During both her pregnancies her water consumption was greatly increased, even at night. According to her husband, this abnormal thirst really was sensational. There was a rapid return to normal after delivery.

E: VII: 5. ♀ b. 1898 in Närkes Kil.

Conductor.

According to her mother and 3 sisters she drinks quite a lot, definitely more than is customary. She suffered from very severe thirst when pregnant — according to her mother, worse than the oldest sister. When the author visited her in 1944, the patient was suffering from a reactive psychosis following the death of 2 sons within a short time of one another. She contested all symptoms in herself and the whole of her family, and refused generally to make any statements. According to local information, her psychosis was so marked that the author considered the evidence of her mother and sisters to be more reliable.

E: VII: 6. ♀ b. 1906 in Närkes Kil.

Conductor.

Interviewed in April 1944. In common with her sisters, the patient has always been thought to be fonder of water than is customary. She supposes she drinks a couple of litres of water a day. Does not wake up at night, but always drinks 2—3 glasses in the morning. Has not been pregnant. Daily output of urine measured in her home $^{12}/_{5}$ and $^{13}/_{5}$ 1944: 2.8 and 2.7 litres respectively.

E: VII: 7. ♀ b. 1910 in Tysslinge, Örebro län.

Conductor.

Interviewed in April 1944. From her childhood the patient has drunk more water than is customary. Knows that this tendency is inherited from her father. Estimates her daily consumption of water at about 3 litres. Drinks one or more glasses at once several times

during the day. Drinking at night is not regular, but it does occur. Always has a drink of water immediately before going to sleep and immediately she wakes up. Intake of water (not other fluid) and output of urine measured in the home: $^{2}/_{5}$ 1944 2.0 litres of water, 3.8 litres of urine. $^{4}/_{5}$ 1.7 litres of water, 3.0 litres of urine.

E: VII: 13. ♂ b. 1892 in Hidinge, Örebro län.

Clinically verified d.i.

Father healthy. The patient has suffered from severe thirst for water since childhood — *i.e.* as long as he can remember. Has not noticed any mitigation of thirst during the last few years. When he was 5 years old, his parent took him to a doctor for his craving for water. He often drinks a litre or more in one draught. Requires to drink and urinate about 3 times every night. Has otherwise always been healthy. No anamnesis for hypertonia.

Investigated at ambulant calls $^{21}/_{10}$ and $^{22}/_{10}$ 1944 at Garphytte Sanatorium. Ruddy, purely pyknomorphic man without dysplasia. No edema. Blood pressure: 260/140. Internal organs and nervous system otherwise normal. Urine normal. Specific gravity 1.001—1.007. Reacts to pituitrin, see diagram fig. 17. In view of the hypertonia he was given a small dose, which was repeated after 2 hours and plainly demonstrated susceptibility to pituitrin.

E: VII: 16. ♂ b. 1897 in Hidinge.

Clinically verified d.i.

Since childhood — that is as far back as he can remember — he has suffered from severe thirst for water, though not so markedly as the brother E: VII: 13. Drinks 4—5 times during the day, sometimes a quarter to half a litre at a time. He does not as a rule wake up at night, though he always has a drink last thing before going to sleep, and always wakes up very thirsty. Has not noticed any mitigation during the last few years. Has always been healthy apart from an eye injury when a child. Investigated at ambulant calls at Garphytte Sanatorium $^{21}/_{10}$ and $^{22}/_{10}$ 1944. Man of average build without dysplasia; fairly lean. No edema. Internal organs normal. Blood pressure: 155/90. Urine normal. Specific gravity: 1.003—1.009. Reacts to pituitrin, see diagram fig. 18.

E: VII: 18. ♂ b. 1902 in Hidinge.

Verified d.i.

Has always drunk a great deal as far back as he can remember; not as much as his brother E: VII: 13, but rather more than E: VII: 16. Does not drink every night, but wakes for a drink several nights during the week. He drinks 3—5 glasses of water immediately on waking in the morning. Can drink more than 1 litre at a time. Has always been generally healthy, apart from hay fever.

Urine sample submitted at a visit to the patient's home in Dec. 1944: according to information received, passed about 4 hours after the last intake of water. Specific gravity: 1.005. 3.51 ‰ NaCl.

E: VIII: 7. ♂ b. 1922 in Tysslinge, d. 1943.

Uncertain diagnosis.

Father healthy. Mother (see above by E: VII: 5) psychotic when interviewed, and denied any thirst disease in the family at all. Neither maternal aunts nor maternal grandmother considered the present case to have had the disease. Treated at Garphytte Sanatorium for 2 months shortly before his death. A fellow patient whom the author has met reported that the patient's consumption of water attracted attention in the ward, and that he was always asking his companions to fill his water bottle. He was said, for one thing, to have drunk a great deal at night.

E: VIII: 8. ♂ b. 1923 in Tysslinge, d. 1944.

Uncertain diagnosis.

Same information from the relations as for his brother. Was also treated at Garphytte Sanatorium before his death. The night nurse on duty in the department has told the author that the patient's consumption of water was very remarkable, and that she had to fill his water bottle several times a night. He also passed large quantities of urine.

E: VIII: 14. ♀ b. 1927 in Garphyttan, Örebro län.

Conductor.

Mother healthy. The patient drinks somewhat more than her brothers, though to no remarkable extent. Likes to drink last thing at night and first thing in the morning. Specific gravity of morning urine $^{21}/_{10}$ 1944: 1.009.

E: VIII: 16. ♀ b. 1939 in Karlskoga, Örebro län, d. 1944.

Conductor.

Mother healthy. According to the information of the parents and 2 paternal uncles, the girl was markedly thirstier than is customary.

Family F.

F: VI: 1. ♂ b. 1846 in Hällefors, d. 1928.

D.i. according to evidence received.

The patient's thirst disease testified to by his widow in a personal interview 1944. 'Drank an absolutely frightful lot of water all his life — got up every night to drink. Always would have a bucket of

Fig. 38. Family F.

water beside his bed'. The patient's abnormal thirst was also known to the children of a half-sister, and testified to by his daughter. On the other hand his son did not know about it. This son is rather feeble-minded.

F: VII: 1. ♀ b. 1906 in Hällefors.

Clinically investigated conductor.

Mother healthy. The patient has on the whole always been healthy, apart from erysipelas in 1940. Has never had albumin in the urine, or other signs of kidney disease. Does not drink more water than other people. Has never needed to drink or urinate during the night. Under observation at the Medical Clinic of the Academic Hospital $^{17}/_{10}$—$^{20}/_{10}$ 1944. A small and lean but otherwise not dysplastic woman. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 125 90. N.P.N.: 28 mgm%. Urine normal. Daily output: 1,000 cc. Water and thirst test, see table 26. Maximal specific gravity: 1.024.

F: V: 8 had 7 sibs, of whom 4 have offspring. No further case has come to light among 96 descendants of these.

Family G.

G: V: 5. ♂ b. 1835 in Hällefors, d. 1911

D. i. according to evidence received.

The patient's thirst disease was described to the author by his niece G: VI: 32 and his nephew G: VI: 34, the latter of whom has himself verified d. i. The uncle and nephew, who knew one another well, had the complaint to about the same extent. The niece G: VI: 32 lived with the patient for a time, and has told the author that her uncle drank copiously, even at night.

G: V: 8. ♀ b. 1841 in Hällefors, d. 1920.

Conductor.

According to the tallying evidence of the daughter G: VI: 32 and the son G: VI: 34, the patient had no symptoms as a rule. During pregnancy, however, she had d. i. symptoms, which at any rate the 4th time were strong, comparable in intensity with the thirst of the male relatives suffering from the complaint. 'It's not strange he should drink so much water, seeing how much I used to drink when I was carrying him' was the mother's constant answer when her son's thirst disease was mentioned.

G: VI: 13. ♀ b. 1869 in Hällefors, d. 1943.

Conductor.

According to her son, he could not remember when she had not drunk more water than is customary, including once every night. Nothing known of the situation during pregnancy. This information was given to a co-worker of the author.

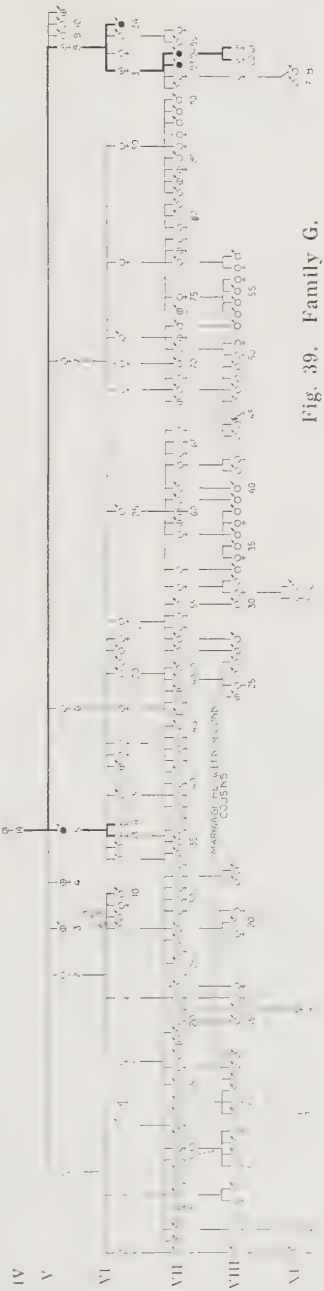


Fig. 39. Family G.

G: VI: 14. ♀ b. 1871 in Hällefors, d. 1899.

Conductor.

The cousins G: VI: 32 and G: VI: 34 had not heard of her having symptoms; nor had her nephew G: VII: 35, who had, however, never met her.

G: VI: 31. ♀ b. 1870 in Hällefors, d. 1944.

Conductor.

Interviewed in November 1943, when she was very senile. Had suffered from mild *diabetes mellitus* for the last 5—10 years. Regulated without insulin. Apart from a short period before the diabetes was regulated she had not been particularly thirsty. Does not remember drinking very much when pregnant. Repeats 'I don't remember anything', but gives fairly detailed information about the thirst disease of her sons. Died 2 months after the interview.

G: VI: 34. ♂ b. 1886 in Hällefors.

Clinically verified d.i.

Father healthy. According to the patient, his mother noticed abnormal thirst in him while he was in the cradle. He drank most before the age of 20 years; at the age of 15 the daily output of urine was 10 litres, at the age of 20 it was 7—8 litres. There was a distinct decrease after the age of 35. The daily output at the age of 57 was about 4—5 litres.

Treated $^{27}/_{9}$—$^{4}/_{11}$ 1908 at the Medical Clinic of the Academic Hospital for *Pneumonia ac. dx.* + *d.i.* Daily output of urine: 3,600—8,850 cc. Average for 35 days: 5,640 cc. Specific gravity: 1.003—1.005.

Otherwise, has always been healthy on the whole.

Under observation at the Medical Clinic of the Academic Hospital $^{8}/_{3}$—$^{17}/_{3}$ 1943, and $^{12}/_{9}$—$^{14}/_{9}$ 1944. Middle-aged pyknic without dysplasia. No edema. Blood pressure: 175/105. Otherwise no signs of disease from internal organs or nervous system. Ecg. normal. N.P.N.: 43 mgm%. Urine normal. Specific gravity: 1.008—1.017. Daily output: 2,800—5,000 cc. Average for 5 days 3,680 cc. Reacts to pituitrin, see diagram fig. 19.

G: VII: 93. ♂ b. 1899 in Stockholm, d. 1902.

D.i. according to evidence received.

His parents and a maternal uncle were interviewed. According to them, he drank at least as much water as the clinically investigated brother, perhaps more. Lived exclusively on water and milk. Lived up to the age of 2 years with his maternal grandmother, at which period her son G: VI: 34 was still at home. This son has reported: 'A. liked me very much because *I* liked water, too. A. was thought to be thirstier than I had been at the same age.'

Treated $^{24}/_{10}$ 1901 to his death $^{18}/_{12}$ 1902 at the hospital Kronprin-

sessan Lovisas Vårdanstalt, Stockholm. From the hospital record:[1] Breast-fed for 7 months. Then received unadulterated milk. Rickets established in February 1901. Was always pale und puny. About $^{10}/_{10}$ 1901, diarrhoea began, with very bad-smelling faeces. On admission: Waxen, flesh lost, constitution extremely weak. Respiratory and circulatory organs: Normal. Abdomen large and meteoric. Liver 2 fingers below the thorax border. Spleen slightly enlarged. *Drinks a great deal.* Urine: No albumin, no sugar. Blood: Hemoglobin 25 %, erythrocytes 1,30 mill.

Body weight: $^{24}/_{10}$ 1901 9,000 gm.

Body weight: $^{9}/_{12}$ 1902 10,970 gm.

Pathological diagnosis: *Anaemia perniciosa progressiva.*

G: VII: 94. ♂ b. 1905 in Stockholm.

Clinically verified d.i.

Father healthy. According to the mother, the patient had 'always' had the thirst disease, and he himself cannot remember when he did not have an intense craving for water. On the whole, the symptoms have remained constant during the years. Drinks and urinates 3—4 times a night. Estimates his daily output at about 7—8 litres. Is an alcoholic psychopathic; has been several times committed to the care of the social services.

Under observation at the Medical Clinic of the Academic Hospital $^{3}/_{5}$—$^{12}/_{5}$ 1943. A man of ordinary build and healthy appearance. No dysplasia and no defects of intelligence. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 135/90. N.P.N.: 30 mgm%. Urine normal. Daily output: 4,000—5,900 cc. Average for 6 days 4,530 cc. Specific gravity: 1,005—1,013. Reacts to pituitrin, see diagram fig. 20.

G: VIII: 60. ♀ b. 1926 in Stockholm.

Clinically investigated conductor.

Mother healthy. According to the mother and maternal grandparents, the patient has drunk a remarkable amount of water since infancy. Wakes up for a drink at least once a night, sometimes 2 or 3 times, when she will drink several glasses full. Does not invariably urinate during the night, but it usually happens once. Otherwise always healthy. Has never had albumin in the urine, or other symptoms of kidney disease. Under observation at the Medical Clinic of the Academic Hospital $^{2}/_{12}$—$^{4}/_{12}$ 1943. Healthy girl with normal constitution and without dysplasia. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 135/75. N.P.N.: 31 mgm%. Urine normal. Water and thirst test, see table 27. Maximal specific gravity: 1,029.

[1] The record citied by kind permission of the head of the clinic, Professor A. Lichtenstein.

$^{30}/_{4}$ and $^{1}/_{5}$ 1944 daily output of urine, measured at home after careful instructions and under her mother's control: 2.5 and 2.6 litres respectively.

G: VIII: 61. ♀ b. 1928 in Stockholm.

Clinically investigated conductor.

According to her mother and maternal grandparents, she has drunk a remarkable lot of water since infancy. Is in the habit of drinking 2—3 glasses after each meal. Drinks a glass or two every night, and urinates once. Has always been healthy. Has not had albumin in the urine, or other signs of kidney trouble.

Under observation at the Medical Clinic of the Academic Hospital $^{2}/_{12}$—$^{4}/_{12}$ 1943. Healthy, normally constituted girl without dysplasia. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 135/80. N.P.N.: 29 mgm%. Urine normal. Water and thirst test, see table 28. Maximal specific gravity: 1.028.

$^{30}/_{4}$ and $^{1}/_{5}$ 1944 daily output of urine, measured at home after careful instructions and under her mother's control: 2.7 and 2.6 litres respectively.

Pedigree H.

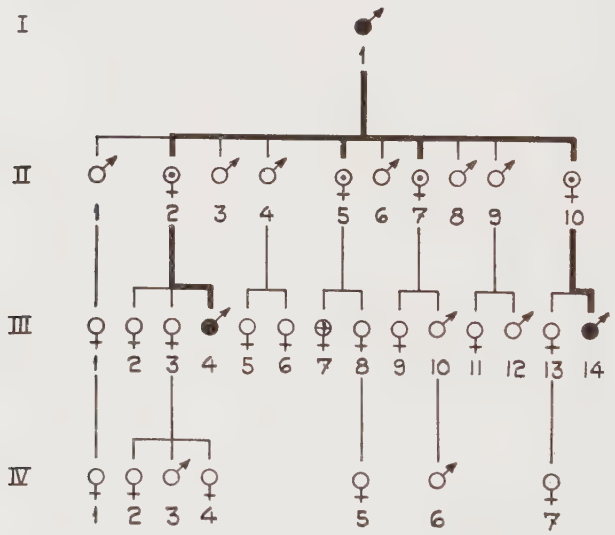


Fig. 40. Pedigree H.

H: I: 1. ♂ b. 1861 in Hjulsjö, Örebro län, d. 1935.

D.i. according to evidence received.

First report was from a man in a neighbouring parish, who was not related to him but who had heard of his great thirst. The author has personally met 3 daughters and 4 grandchildren of the patient.

Apparently he always had a great craving for water; would get up to drink several times a night, and could empty a whole 1-litre scoop at a draught. The thirst diminished somewhat in his old age.

H: II: 2. ♀ b. 1886 in Grangärde.

Conductor.

Mother healthy. The patient was interviewed in May 1943. Has always been healthy, apart from a tendency for eczema. Has not had albumin in the urine, or other signs of kidney disease. Drinks more water than is customary, but much less than her father and son. Gets up once or twice a night to drink and urinate, somewhat oftener after her last pregnancy. As far as she now remembers, she was not particularly thirsty during her first pregnancy. There was a considerable increase of thirst towards the end of her second, and towards the end of the third she drank at least as much as the son did subsequently, — several times a night, for instance. After partus there was a rapid return to her usual state, though the last time the return was not complete. In May 1944 a daily output of urine measured in the home was 1.8 litres.

H: II: 5. ♀ b. 1893 in Grangärde.

Clinically investigated conductor.

Has on the whole always been healthy. Has always needed more water than others. Has from a child been in the habit of drinking at least once a night, most often twice and has large outputs of urine; claims to have passed up to 1 1/2 litres at once. Has noticed a distinct decrease in her thirst during the last few years. Has gone through 2 pregnancies, and been extremely thirsty both times, to about the same degree as her father. During these times she used to get up 3—5 times a night to drink and urinate. Immediately after partus, her thirst resumed its normal proportions. Under observation at the Medical Clinic of the Academic Hospital 13/3—16/3 1944. Pyknomorphic woman, moderately corpulent, not dysplastic. No edema or other signs of incompensation. Blood pressure: 170/95. Ecg.: Bundle branch block. Otherwise no signs of disease from internal organs or nervous system. N.P.N.: 35 mgm%. Urine normal. Daily output: 2,800 cc which were measured, added to which is a quantity lost during defaecation, estimated by the patient at 500 cc.[1] Specific gravity of night urine during 2 nights without thirst test: 1.010. Water and thirst test, see table 29. Maximal specific gravity: 1.023.

H: II: 7. ♀ b. 1898 in Grangärde.

Conductor.

Has always been healthy on the whole. No albumin or other signs of kidney diseases. Has always drunk a great deal of water since

[1] This output of 24 hours in table 16 is taken to be 3,000 cc.

childhood. Has always urinated once during the night, and more often than not drunk a couple of glasses of water during the night. Cannot remember that her thirst was worse during her pregnancies. Daily output of urine measured at home in May 1944: 2.5 litres.

H: II: 10. ♀ b. 1906 in Grangärde, d. 1939.

Conductor.

According to her son and her 3 sisters, this case showed no abnormal thirst. Nothing known of the situation during pregnancies.

H: III: 3. ♀ b. 1919 in Grangärde.

Probable conductor.

Not determinable *a priori* as a heterozygote. No symptoms when not pregnant. During the end of her second pregnancy her thirst was plainly increased. During the last part of her third pregnancy 1943—1944 her thirst was very strong; she woke up many times a night to drink and urinate. The symptoms ceased abruptly after partus. In the light of these symptoms, it is probable that the patient is a heterozygote.

H: III: 4. ♂ b. 1922 in Grangärde.

Clinically verified d.i.

Father healthy. The patient has always drunk a great deal of water for as long as his parents and he himself can remember; he estimates his intake as an adult at 10—15 litres per 24 hours. Usually drinks a good litre at a time. Wakes up at least once a night, when he drinks 1—2 litres and urinates. Has otherwise always been healthy physically. According to information received he is a mythomanic psychopath.

Under observation at the Medical Clinic of the Academic Hospital $^{16}/_{8}$—$^{28}/_{8}$ 1943. Leptomorphic youth without dysplasia. General condition good. No edema. No signs of defective intelligence. No abnormality in interior organs or nervous system. Blood pressure: 130/75. N.P.N.: 31 mgm%. Urine normal. Daily output: 6,800—9,540 cc. Mean for 8 days: 8,300 cc. Specific gravity: 1.001—1.007. Reacts to pituitrin, see diagram fig. 21.

H: III: 14. ♂ b. 1927 in Grangärde.

Clinically verified d.i.

Father healthy. As far back as he can remember, the patient has always drunk more than others, and has urinated plentifully. Suffered from considerably less marked thirst, however, than the cousin H: III: 4, with whom he lives. Gets up 2—3 times a night to drink and urinate. Can easily drink 1 litre or more at a time.

Under observation at the Medical Clinic of the Academic Hospital $^{24}/_{1}$—$^{27}/_{1}$ 1944. Chubby boy of healthy appearance and normal level of development. No edema. No signs of disease from the internal organs or nervous system. Blood pressure: 120/70. N.P.N.: 32 mgm%. Urine normal. Only complete output during 24 hours: 3,600 cc. Specific gravity: 1.003—1.012. Reacts to pituitrin, see diagram fig. 22.

Pedigree J.

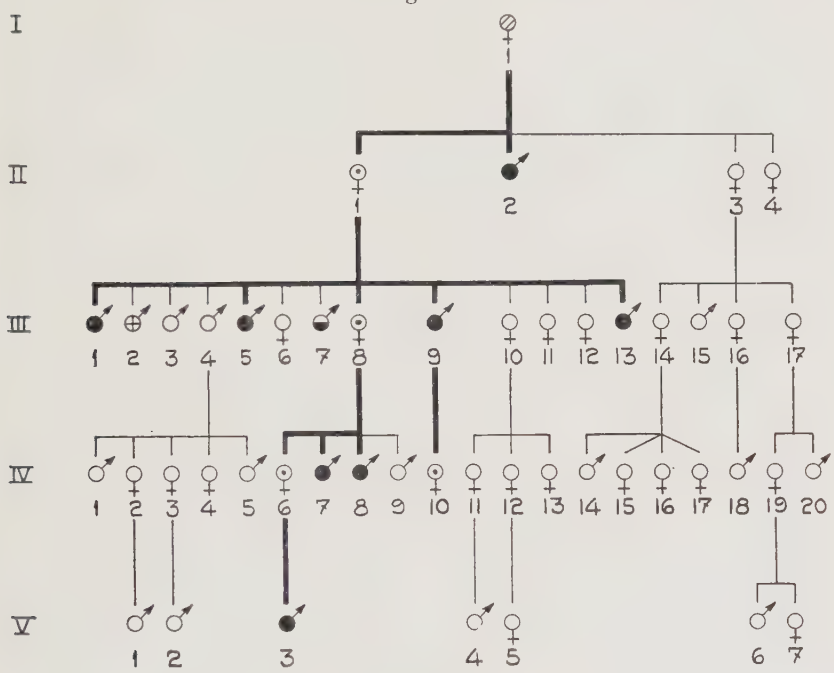


Fig. 41. Pedigree J.

J: II: 1. ♀ b. 1852 in Gryta, Uppsala län, d. 1929.

Conductor.

According to the daughter J: III: 8 and the son J: III: 9, she showed no symptoms. Nor was she thought to have shown abnormal thirst in any of her numerous pregnancies. When the youngest child was born, the daughter J: III: 8 was 12 years old, and still living at home. If the conspicuous symptom of *d.i. gravidarum* had been present, it is probable the daughter would have known about it.

J: II: 2. ♂ b. 1854 in Gryta, d. 1876?

D.i. according to entries in hospital records.

Not known by any person now living. Hospital records of J: III: 5 from 1897 have the unqualified entry that he had d.i. 'A maternal

uncle of the patient's took his life by hanging himself at the age of 22 years. This uncle suffered from d. i.' Another entry runs: 'Suffered from diabetes, probably congenital'. The same records moreover contain correct data as to all the 13 children of his sister J: II: 1, but also a report that the father of the 13 was reputed to drink a great deal of water 'almost every hour'. According to the tallying evidence of the children now living, and of other more distant relations, this later report is incorrect. However, J: II: 2's d.i. is also mentioned in records at the Surgical Clinic in 1905, these, too, dealing with J: III: 5. As the incorrect report as to the thirst of the 13 children's father is not repeated in this record, and as the 2 anamneses differ in a number of other respects also, there is reason to suppose that the record from 1905 was, at any rate in part, made independent of the older record. As, therefore, the d.i. of the present case has been testified to on two different occasions, 8 years apart, the diagnosis has been accepted.

J: III: 1. ♂ b. 1872 in Gryta, d. 1936.

Clinically verified d.i. + Oligophrenia.

Treated at the Academic Hospital $^{14}/_{3}$—$^{26}/_{5}$ 1936 on the diagnosis: *Scorbut + d.i. + myocarditis chron. + cystopyelitis.*

Has been mentally backward since childhood. All his life the patient had drunk a great deal of water, and passed great quantities of urine. The month before admission to hospital he had shown a general decline with loss of appetite and weight. Lived on coffee and buns. Bruised extensively.

State on admission: Imbecile. Thin and dessicated. The legs showed efflorescences, which a test excision proved to be small haemorrhages at the hair follicles. As well as this there were larger suggillations. The gingiva was swollen with a tendency to bleeding. No general edema. Signs of thrombosis in the left leg. Physical examination of heart and lungs showed nothing abnormal, but the ecg. revealed signs of myocardium injury. Blood pressure: 125/80. No sugar or albumin in the urine. Hemoglobin 50 %; erythrocytes: 2.48 mill.; thrombocytes: 184,000. Clot retraction normal. No petechiae revealed by Göthlin's test. The skin haemorrhages gradually disappeared during treatment with ascorbic acid.

The patient, who was apathetic during his stay in hospital, had frequently to be catheterized. The urinary tract soon became infected with colon bacilli, pus and small quantities of albumin appearing in the urine; there were also periods of fever. Daily output of urine: 4,100—10,600 cc. Mean for 46 days: 7,870 cc. Specific gravity 1.003—1.009. During a 6-hour thirst test the specific gravity did not exceed 1.008. On one occasion 5,500 cc of urine were drained off with a bladder catheter.

After rather more than 2 months in bed, the patient contracted broncho-pneumonia and died. There were smaller outputs of urine during the last week of life: 2,500—4,600 cc.

Repeated periods of fever did not lower the diuresis at all, nor did amidopyrine. Hormone therapy was not tried.

As to patho-anatomy, see page 93.

J: III: 5. ♂ b. 1879 in Gryta, d. 1905.

Clinically verified d.i. + Oligophrenia.

The father reputed healthy. The patient treated at the Medical and Surgical Clinics of the Academic Hospital $^{15}/_{12}$ 1897—$^{7}/_{2}$ 1898 on the diagnosis: *d.i. + bronchitis acuta + conjunctivitis acuta purulenta.* Was again at both clinics of the same hospital $^{3}/_{11}$—$^{14}/_{11}$ 1905 for *d.i. + cystitis chronica + pyelonephritis acuta.*

As far back as he could remember, he had always drunk a great deal of water and needed to urinate 6—7 times a day and 3—4 times a night. Had not been able to keep up at school, and was very surly.

From the state on admission 1897: Intelligence not very well developed. Bodily constitution fairly good. Genitals normal. Heart and lungs normal. Urine: No sugar, no albumin. Daily output: 4,650—11,000 cc. Mean for 41 days: 7,490 cc. Specific gravity: 1.002—1.003.

When admitted to the Surgical Clinic in 1905 he had acute trouble in the urinary tract with difficulty in urinating, blood in the urine and pain, fever, pyuria and acute symptoms from the right kidney. On $^{10}/_{11}$ he underwent nephrostomy on the right side, when numerous small abscesses were revealed in the kidney. The patient died 4 days after the operation from what, according to the description, was uraemia: The amount of urine passed became much less, the patient contracted facial twitches, diarrhoea, and crystals on the skin. The autopsy revealed very greatly enlarged kidneys with large numbers of miliary abscesses.

J: III: 7. ♂ b. 1883 in Gryta, d. 1884.

Possibly d.i.

The records from 1897 over J: III: 5 contain the following entry about the present case: 'Died at the age of 1 $^{1}/_{2}$ years; weaned after the 4th month; drank a great deal'. The brother J: III: 9 has told the author that the patient was thought to have the thirst disease. The sister J: III: 8 has no information to give on this point.

J: III: 8. ♀ b. 1885 in Gryta.

Conductor.

Has met the author several times, and told him that she does not drink more water than other people. Nor was she particularly thirsty during any of her 4 pregnancies.

Treated at the Medical Clinic of the Academic Hospital in 1925 on the diagnosis: *Cholelithiasis + neurosis.* Normal type of constitution. Blood pressure: 125/80. Cholelithiasis verified by roentgen. Otherwise no signs of disease from internal organs, or from the nervous system. No albumin, no sugar. Specific gravity: 1.019—1.026. Largest daily output of urine measured: 1,300 cc.

J: III: 9. ♂ b. 1888 in Gryta.

Clinically verified d.i. + diabetes mellitus + schizophrenia.

Treated at the Medical Clinic of the Academic Hospital $^{27}/_{3}$—$^{27}/_{4}$ 1935, $^{17}/_{9}$—$^{17}/_{10}$ 1941, and $^{22}/_{3}$—$^{24}/_{3}$ 1943.

As far back as he can remember he has always had a great craving for water, and drunk great quantities, 10—15 litres daily. Has passed great quantities of urine. He wakes up twice a night to drink and urinate. Drinks 1—2 1-litre scoops at a time.

Is said to have got through school quite well. Since about the age of 30 years he has suffered from auditory hallucinations and other signs of a fairly mild paranoid schizophrenia.

From Christmastide 1934 he was tired and still thirstier than before. On admission to the hospital in March 1935, the internal organs and nervous system were normal. Blood pressure: 145/110. His urine was almost water-clear, with a specific gravity of 1.008, and containing 0.31 % sugar. The blood sugar values varied during 1 day and night between 0.100 and 0.167 %. Free from acidosis the whole time. After the content of carbohydrates in the diet had been reduced, the urine rapidly became free from sugar, and the thirst was subjectively reduced to its usual degree. The daily outputs of urine varied between 6,400 and 15,300 cc. Specific gravity: 1.005—1.007. (The figure of 1.007 was not exceeded in a thirst test of 12 hours duration, performed with considerable discomfort to the patient and a loss in weight of 5.4 kg). The urine was free from albumin the whole time, and the sediment normal.

The general condition of the patient while under hospital observation the two last times was good. He is heavily built and with a primitive face, but without any very great dysplasia. No signs of disease from internal organs. Urine free from sugar, or with only slight traces. No albumin. Sediment normal. Blood pressure: 120/80. 1941 glycose tolerance test: Pathological curve with raised initial value and prolonged decline. Daily output of urine 5,200—12,000 cc; mean for 18 days: 8,590 cc. Specific gravity: 1.003—1.006.

Totally unaffected by repeated tests with different preparations from the pituitary posterior lobe, see diagrams fig. 23 and 25.

J: III: 13. ♂ b. 1896 in Gryta, d. 1898 aged 2 1/2 years.

D.i. according to evidence received.

From the records made in 1897 of J: III: 5: 'Three of the patient's brothers seem to suffer from the same complaint as he does . . . The third is the youngest child, aged 1 year, who also drinks a great deal'. The author has met 2 sibs who have given tallying evidence of his great thirst. The sister J: III: 8 looked after him before he died from meningitis, 'and surely I ought to know what an enormous lot he drank'.

J: IV: 6. ♀ b. 1913 in Upsala.

Clinically investigated conductor.

Father healthy. The patient to her own knowledge has always been healthy, on the whole. Has not had kidney trouble, or albumin in the urine.

Not fonder of water than people usually are. Never drinks during the night. Suffered from thirst during her hitherto only pregnancy, above all at the beginning, when she also vomited a great deal. Was far less thirsty during the last months.

Under observation at the Medical Clinic of the Academic Hospital 1/12—3/12 1943. Normally built young woman of healthy appearance. No signs of disease from internal organs or nervous system. No edema. Blood pressure: 110/75. N.P.N.: 34 mgm%. Urine normal. Water and thirst test, see table 30. Maximal specific gravity: 1.014.

J: IV: 7. ♂ b. 1914 in Upsala, d. 1915 aged 1 year 5 1/2 months.

D.i. according to evidence received.

According to the mother the patient was always thirsty. He screamed a great deal, and was quiet only if he was given some water. Passed large quantities of urine. Grew only in height, and became very thin. A doctor was consulted, and he prescribed rationing the amount of water given the child; this could not be kept to. The mother had 3 other children, 1 with certain d.i. and 2 without; she considers this 4th child to have been unquestionably suffering from the disease. The cause of death was given as a disease of the blood.

J: IV: 8. ♂ b. 1921 in Upsala.

Clinically verified d.i. + Oligophrenia.

Has had a strong thirst since he was quite small. Has always drunk and urinated twice a night. From childhood has been generally puny and somewhat backward. Did not walk until he was over 2 years old. Started talking at the normal time. Otherwise healthy on the whole. Treated at the Children's Clinic of the Academic Hospital 30/10—12/11 1930. Thin boy without dysplasia. Weight: 25 kg.

No signs of disease from internal organs or nervous system. No edema. Blood pressure: 105/75. Urine normal. Daily output: 2,900—6,600 cc. Mean for 12 days: 4,790 cc. Specific gravity: 1.006—1.014. Treatment with pituitrin had no effect, see diagram fig. 26.

Investigated in ambulant calls by the author in January 1941 and January 1944. Ordinary constitution, on the thin side. Gives an impression of slight *debilitas mentis*. No signs of disease from internal organs or nervous system. Urine measured for 2 nights (8 hours): 2,750 and 2,500 cc. Specific gravity: 1.002—1.003. Refractory to pituitrin, see diagram fig. 24. Measured output 2 days in Nov. 1944: 12,320 and 13,110 cc respectively.

J: IV: 10. ♀ b. 1931 in Vänge, Upsala län.

Clinically investigated conductor.

Mother healthy. The patient was treated at the Ophthalmic Clinic of the Academic Hospital for dacryocystitis. Has otherwise always been healthy, on the whole. Does not drink more water than other people. Never drinks at night. Her stepfather considers her to have drunk rather a lot of water as a child — a pretty vague statement.

Under observation at the Medical Clinic of the Academic Hospital $^{3}/_{8}$—$^{5}/_{8}$ 1942 and $^{1}/_{2}$—$^{3}/_{2}$ 1944. Healthy girl with normal constitution. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 130/80. N.P.N.: 39 mgm%. Inulin clearance 118.6 cc/min. Hippuran clearance (an iodine containing substance): 495 cc/min. Thirst test $^{4}/_{8}$ 1942, 8 a.m. to 6.30 p.m. Maximal specific gravity: 1.018. Water and thirst test 1943, see table 31. Maximal specific gravity: 1.019.

J: V: 3. ♂ b. 1941 in Stockholm.

Clinically verified d.i.

Father healthy. Patient treated at the Medical Department of Kronprinsessan Lovisas Vårdanstalt, Stockholm, $^{15}/_{10}$ 1943—$^{3}/_{2}$ 1944 on the diagnosis d.i.[1]

After being weaned he has always been difficult with his food; likes liquid fare, but refuses to take anything solid. Has therefore been kept on the diet of a 1-year-old even up to the age of 2 years 4 months. Was very thirsty, and received about 1 litre of liquid a day, apart from his milk. Passed large quantities of urine. After the age of 6 weeks has always vomited a little after being fed. Constipated since birth. Very backward in general development. Weight at birth: 3,200 gm, at 1 year: about 6.0 kg, at 2 years 4 months: 7,030 gm. Height: 75 cm.

Spoke a few odd words at the age of 10 months, after which he made no further progress in speaking. At the age of 2 years 4 months

[1] The record citied by kind permission of the head of the clinic, Professor A. Lichtenstein.

he can sit up by himself, and walk and stand with support, but not without.

A very small and extremely thin child with lowered turgor. No cyanosis or dyspnoea, colour of skin good. Screams lustily. Pharynx, lymph glands, heart and lungs normal. Liver by the arcus, spleen not palpable. No edema. Urine normal. Babinski positive bilaterally; otherwise nothing abnormal from the nervous system.

Roentgen of gastro-intestinal canal: Normal. Skeleton roentgen: Normal development of epiphyses and ossification centres.

The sella turcica normal. Roentgen of heart normal: Ecg.: No certain pathological signs. Glycose loading normal.

Fractious when thirsty during his whole time in hospital; drinks greedily, and can take 100 cc at a draught, after which he becomes calm and still again. Daily output of urine about 1,000 cc; intake of water about 1,600 cc. — Thermolabile with several fairly marked rises of temperature without noteworthy catarrhal symptoms. Specific gravity: 1.002—1.008. For reaction to pituitrin, see p. 90.

Pedigree K.

K: I: 1. ♂ b. 1837 in Strängnäs, Södermanlands län, d. 1897.

D.i. according to evidence received.

According to the daughter K: II: 2, and the son K: II: 3 their father definitely suffered from thirst disease, and their mother did not. The daughter remembers hearing it said about herself that she had inherited her severe thirst from her father. Remembers no details otherwise.

K: II: 2. ♀ b. 1864 in Vittinge, Västmanlands län.

Verified d.i.

Has always drunk more water than others; knows that she did so while still a child. Used to have a water bottle by the bed at night. A granddaughter and a son testify that she used previously to drink 2 litres a night. Her thirst diminished considerably in her old age, so that she no longer needs to drink every night. Still drinks several glasses of water as soon as she wakes up in the morning.

When she was pregnant, her thirst increased considerably. She remembers that the midwife attending her at one delivery tried to prevent her drinking so much. After the delivery her thirst decreased.

5/10 1944. Investigated in her home. An old woman with chronic joint changes, but otherwise healthy. On the day of the investigation she had had a drink in the morning about 7, subsequently, on her own showing, not drinking anything else except 2 cups of coffee —

this relative debarment from water was not controlled, however. Urine sample 11.45 a.m.: Specific gravity: 1.006, 2.09 ‰ NaCl. Urine otherwise normal.

K: III: 7. ♂ b. 1892 in Härkeberga, Upsala län.

Clinically verified d.i. + Oligophrenia.

Father healthy. The patient has had a strong thirst ever since he can remember — always, according to his mother. As a rule he drinks and urinates twice a night, sometimes only once. Always

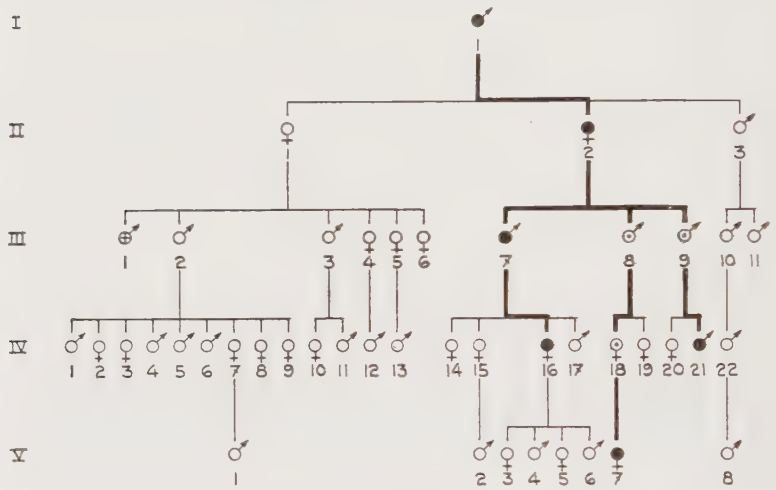


Fig. 42. Pedigree K.

wakes up very thirsty. Drinks 2—3 glasses at a time, but never as much as a litre.

Treated at the Medical Clinic of the Academic Hospital $^{8}/_{2}$—$^{13}/_{3}$ 1936 on the diagnosis: *Anaemia secundaria + Polydipsia et polyuria.* On admission: hemoglobin 50 %, erythrocytes 2.41 mill., s.r. 85 mm/hour. No signs of haemorrhage from the digestive tract. Recovered without etiological diagnosis. No dysplasia. No edema. Blood pressure: 120/70. N.P.N.: 35 mgm%. Urine normal. Daily output: 2,000—4,500 cc. Mean for 10 days: 3,810 cc. Specific gravity of daily outputs: 1.006—1.012. In the thirst test he reached the specific gravity: 1.018, in water loading and thirst test: 1.017.

Again under observation at the Medical Clinic of the Academic Hospital ^{23} 9—^{25} 9 1944. General condition good. Gives an impression of moderate debilitas mentis. Internal organs and nervous system normal. No edema. Blood pressure: 140/80. N.P.N.: 30 mgm%.

Urine normal. Only complete 24-hour output: 2,500 cc. Specific gravity: 1.007—1.010. Reacts to pituitrin, see diagram fig. 29.

K: III: 8. ♂ b. 1896 in Härkeberga.

Conductor.

According to his mother, a daughter, and other relations, he does not drink more than people usually do. Never drinks during the night. Submitted sample of morning urine $^{12}/_{10}$ 1944: Specific gravity: 1.020. 6.20 ‰ NaCl. Urine otherwise normal.

K: III: 9. ♂ b. 1900 in Härkeberga.

Clinically investigated male conductor.

Always been healthy on the whole. Does not differ from others in his water requirements. Never drinks or urinates during the night.

Under observation at the Medical Clinic of the Academic Hospital $^{12}/_{10}$—$^{14}/_{10}$ 1944. Normally built middle-aged man with good general condition. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 135/85. N.P.N.: 38 mgm%. Urine normal. Water and thirst test, see table 32. Maximal specific gravity: 1.028.

K: IV: 16. ♀ b. 1917 in Enköping, Upsala län.

Clinically verified d.i. and d.i. gravidarum.

Mother healthy. The patient herself has always been healthy on the whole. To her knowledge, she has never had albumin in the urine or other signs of kidney disease, except at her first delivery.

During childhood and before her pregnancies, her water consumption was completely normal. She does not herself remember being particularly thirsty during her 1st and 2nd pregnancies, but according to information from her husband and a sister, this was so.

Treated at the Obstetric Clinic of the Academic Hospital $^{12}/_{1}$—$^{19}/_{1}$ 1936 for her first delivery, which took place $^{12}/_{1}$. Diagnosis: *Graviditas. Albuminuria gravid.* + *Albuminuria sub et post part.* Owing to the albuminuria, her outputs of urine were measured. The greatest amount was 4,000 cc. Average for 7 days: > 2,370 cc (expressed thus because, according to the notes, most of the daily outputs are not fully recorded). No data as to specific gravity.

There are no objective data as to the amount of urine during the 2nd pregnancy in 1937. The urine was free from albumin at and after delivery.

During the latter part of the 3rd pregnancy, her thirst increased markedly, so that she began drinking at night, also. According to her husband and sister, her drinking was really astounding even at this

time. The great increase of thirst ceased on delivery, but there was no complete return to normal. There are no figures for urine, etc.

Pregnant for the 4th time in 1943, with last menses 1/3. From September onwards, she suffered very severe thirst, which increased up to delivery on 14/12. The last month she drank copiously, at least once an hour during the night, when she also urinated. Her husband estimates her nightly water consumption at about 4 litres.

Treated at the Obstetric Clinic of the Academic Hospital 7/12—20/12 1943. Before partus, the lowest daily output of urine was 4.000 cc, and the highest 6.800 cc. Mean for 7 days: 5,750 cc. Mean for the week immediately following delivery: 3.870 cc. During water and thirst test, she did not reach a specific gravity of over 1.008. See table 33. The test was interrupted after 12 hours by labour.

Under observation at the Medical Clinic of the Academic Hospital 21/12—23/12 1943. Normally built young woman without dysplasia. No edema. No signs of disease from internal organs or nervous system. Blood pressure: 120/75. N.P.N.: 36 mgm%. Urine normal. During these few days at the Clinic she still had a plainly pathological thirst; a daily output of urine of 3,570 cc was measured. Subjectively, the thirst had improved considerably after delivery. On the day of her discharge she was given 1 ml Hypadrin, after which she was unable to produce any samples of urine for 2 1/2 hours. Her thirst ceased for the whole day.

Again under observation 12/10—14/10 1944. Is still nursing and menstruation has not recommenced, but the patient shows no subjective or objective signs of pregnancy. After her last delivery, her thirst increased steadily during the first month, but has never resumed normal proportions. At present, she drinks 6—8 glasses of water a day, and wakes up once a night to urinate and drink 1—2 glasses. Feels quite healthy otherwise. Objective general condition unchanged. Blood pressure: 120/85. Urine normal. Water and thirst test, see table 34. Highest specific gravity: 1.016.

K: IV: 18. ♀ b. 1921 in Härkeberga.

Clinically investigated conductor.

Mother healthy. In 1941 the present case had an acute pyelitis, with albumin in the urine. Has otherwise never had kidney trouble. Has had peritonsillitis several times, but has otherwise always been healthy. No abnormal water requirements as a child and girl. At the end of her hitherto only pregnancy in 1943 the patient contracted severe thirst, which got worse and worse. The last months of pregnancy she drank 5—6 litres of water a day, and 1 litre at night. The information is fairly trustworthy, as she used to drink from a scoop which held a litre. Sometimes she drank so much that she brought the water up again, but had to have another drink at once.

Passed very large quantities of urine, and urinated several times a night. Her copious drinking attracted attention in the family, who confirmed the patient's information to the author. As soon as the labour pains began, the severe thirst ceased. After delivery she returned to fully normal water requirements.

Under observation at the Medical Clinic of the Academic Hospital $^{12}/_{10}$—$^{14}/_{10}$ 1944. Healthy young woman without dysplasia. Internal organs and nervous system normal. No edema. Blood pressure: 110/70. Water and thirst test, see table 35. Maximal specific gravity: 1.034.

K: IV: 21. ♂ b. 1928 in Enköping.

Clinically verified d.i. + Oligophrenia.

Mother healthy. The patient has been very addicted to water drinking from earliest childhood. Till he was about 8 years old, he had to be woken up so as not to urinate in the bed. He then used to have a drink at the same time. Has not had enuresis subsequently, and does not need to drink during the night. Always wakes up very thirsty, and drinks constantly during the day, often a whole 1-litre scoop at a time, and probably 2—3 litres per 24 hours.

Backward in development. Late in learning to walk and speak. Attended a Special School for mental defectives. Has otherwise been generally healthy, physically.

Under observation at the Medical Clinic of the Academic Hospital $^{12}/_{10}$—$^{14}/_{10}$ 1944. Debile boy, small for his age, but not otherwise dysplastic. No edema. No signs of disease from internal organs or nervous system, apart from a nystagmus of congenital type. Blood pressure: 135/80. N.P.N.: 30 mgm%. Urine normal. Thirst test carried out under control from 9 p.m. on $^{12}/_{10}$ to 12 noon on $^{13}/_{10}$, at the end of which time the patient was showing real distress. Specific gravity of morning urine: 1.009. Maximal specific gravity: 1.013. Only measured daily output: 3,320 cc (the last 4 hours of the thirst test is included in the period of 24 hours during which the output was measured).

K: V: 7. ♀ b. 1943 in Enköping.

D.i. according to anamnesis.

Father healthy. Patient observed in her home at the age of 11 months. During the period she was suckled, *i.e.* 6 months, she received no extra water. After weaning, she woke regularly twice a night, and cried. Was quiet and went to sleep only if she was given water. At her present age of 11 months she now begs for water all day. Drinks 1—2 coffee-cups full after her meals.

Pedigree L.

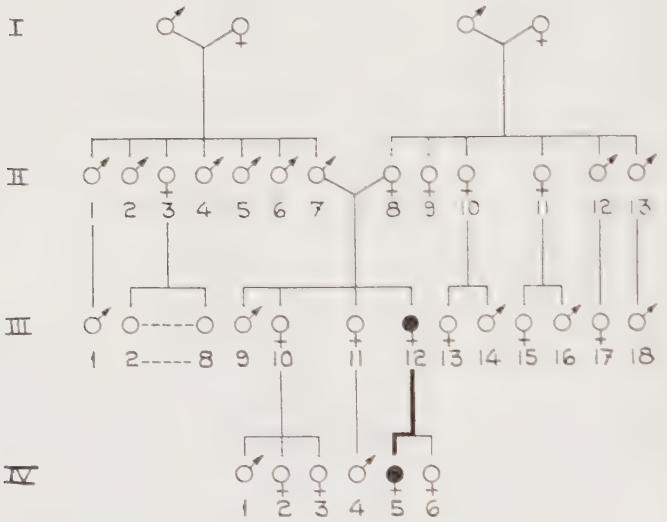


Fig. 43. Pedigree L.

L: III: 12. ♀ b. 1914 in Stockholm.

Clinically verified d.i.

Both parents healthy. Thirst disease reputedly revealed in the patient before she could speak. As an adult she has consumed between 12—15 litres of water per 24 hours. No mitigation during occasional fevers. Has had one early abortion and 2 full-term pregnancies. Her thirst grew even more intense during pregnancies. She herself states that the symptoms were most severe in the 4th month. Has otherwise had no major diseases. Treated at the Gynaecological Clinic at Lund Hospital $^{12}/_{1}$—$^{9}/_{2}$ on the diagnosis: d.i. Was then in the 5th month of pregnancy. Urine outputs varied between 10 and 20 litres.

Under observation at the Medical Clinic of the Academic Hospital $^{6}/_{4}$—$^{9}/_{4}$ 1943. Pyknomorphic young woman in good general condition. No edema. Signs of diffuse bronchitis. Otherwise no signs of disease from internal organs or nervous system. Blood pressure: 140/80. N.P.N.: 24 mgm%. Urine normal. Daily outputs: 11,600 and 8,100 cc. Specific gravity: 1,000—1,003. Reacts to pituitrin, see diagram fig. 30.

L: IV: 5. ♀ b. 1936 in Nyköping, Södermanlands län.

Clinically verified d.i.

Father healthy. The thirst disease of the patient was revealed before she could speak. Always drinks copious quantities of water. Gets up 3—4 times a night to drink and urinate. Her mother has not noticed any falling off of the symptoms during occasional fevers. Has otherwise always been healthy on the whole.

Under observation at the Medical Clinic of the Academic Hospital $^{6}/_{4}$—$^{9}/_{4}$ 1943. Healthy girl, with an appearance normal for her age. Internal organs and nervous system normal. Urine normal. Body weight 29 kg. Daily outputs: 4,450 and 3,900 cc. Specific gravity: 1.001—1.005. Reacts to pituitrin, see diagram fig. 31.

Water and thirst tests.

Table 21.

B: VI: 31. Water and thirst test. 1,000 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	55	1.019
8	60	1.011
8.30	95	1.003
9	115	1.002
9.30	105	1.002
10	—	—
	375	
10.30	215	1.003
11	30	1.005
11.30	80	1.004
12 noon	50	1.007
	750	
2 p.m.	115	1.008
4	65	1.010
6	110	1.012
8[2]	75	1.013
8 a.m.	260	1.018
	1,375	

[1] Body weight 68.7 kg.
[2] „ „ 67.8 „ .

Table 22.

B: VIII: 22. Water and thirst test. 1,500 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	75	1.029
8	no sample	—
8.30	405	1.008
9	495	1.003
9.30	540	1.001
10	445	1.002
	1,885	
10.30	230	1.004
11	no sample	—
11.30	„ „	—
12 noon	110	1.012
	2,225	
2 p.m.	130	1.015
4	60	1.020
6	45	1.023
8	45	1.026
8 a.m.[2]	155	1.031
	2,660	

[1] Body weight 75.6 kg.
[2] „ „ 73.7 „.

Table 23.

B: VIII: 23. Water and thirst test. 1,000 cc water given at 7 a.m. Temperature in the room during the test 22° C.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	180	1.026
8	110	1.008
8.30	250	1.002
9	300	1.002
9.30	260	1.002
10	280	1.002
	1.200	
10.30	125	1.006
11	50	1.009
11.30	70	1.010
12 noon	60	1.012
	1.505	
2 p.m.	100	1.020
4	65	1.024
6	75	1.023
8	50	1.027
8 a.m.[2]	165	1.029
	1,960	

[1] Body weight 48.2 kg.
[2] „ „ 46.8 „ .

Table 24.

C: VII: 4. Water and thirst test. 1,500 cc water given at 8 a.m., 200 cc at 6 p.m. and 100 cc at 8 p.m. Temperature in the room during the test, 26° C.

Time	*Urine cc*	*Specific gravity*
7 a.m.	500	1.009
8[1]	135	1.006
8.30	280	1.005
9	350	1.003
9.30	160	1.003
10	65	1.004
	990	
10.30	120	1.004
11	115	1.005
11.30	105	1.005
12 noon	65	1.008
	1,395	
2 p.m.	175	1.010
4	30	1.012
6	135	1.011
8	70	1.015
8 a.m.[2]	585	1.014
	2,390	

[1] Body weight 56.1 kg.
[2] „ „ 54.8 „ .

Table 25.

C: VIII: 8. Water and thirst test. 1,200 cc water given at 8 a.m. and 200 cc at 6 p.m. Temperature in room during the test, 26° C.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	45	1.010
8	130	1.006
8.30	185	1.003
9	290	1.003
9.30	250	1.003
10	90	1.004
	945	
10.30	100	1.004
11	60	1.006
11.30	65	1.007
12 noon	95	1.008
	1,265	
2 p.m.	315	1.008
4	30	1.015
6	75	1.011
8	85	1.013
8 a.m.[2]	390	1.018
	2,160	

[1] Body weight 57.6 kg.
[2] „ „ 56.8 „

Table 26.

F: VII: 1. Water and thirst test. 1,200 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	70	1.017
8	120	1.007
8.30	430	1.001
9	510	1.000
9.30	210	1.003
10	60	1.006
	1,330	
10.30	40	1.008
11	25	1.008
11.30	30	1.012
12 noon	35	1.012
	1,460	
2 p.m.	65	1.015
4	100	1.014
6	65	1.019
8	50	1.022
8 a.m.[2]	200	1.024
	1,940	

[1] Body weight 39.7 kg.
[2] „ „ 38.6 „ .

Table 27.

G: VIII: 60. Water and thirst test. 1,500 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.	110	1.012
8 [1]	210	1.004
8.30	360	1.000
9	360	1.000
9.30	210	1.001
10	115	1.002
	1.255	
10.30	125	1.003
11	80	1.004
11.30	65	1.006
12 noon	30	1.011
	1.555	
2 p.m.	70	1.017
4	50	1.019
6	45	1.029
8	40	1.028
8 a.m. [2]	190	1.029
	1,950	

[1] Body weight 60.4 kg.
[2] „ „ 58.8 „

Table 28.

G: VIII: 61. Water and thirst test. 1,500 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.	80	1.014
8 [1]	155	1.005
8.30	330	1.001
9	330	1.001
9.30	280	1.001
10	180	1.002
	1,275	
10.30	240	1.002
11	135	1.003
11.30	110	1.005
12 noon	70	1.006
	1,830	
2 p.m.	145	1.011
4	50	1.019
6	50	1.025
8	45	1.028
8 a.m.[2]	200	1.028
	2,320	

[1] Body weight 59.5 kg.
[2] „ „ 57.7 „ .

Table 29.

H: H: 5. Water and thirst test. 1,500 cc water given at 7 a.m. and 40 cc at 8 p.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	60	1.014
8	240	1.006
8.30	290	1.002
9	290	1.002
9.30	200	1.003
10	135	1.004
	1,155	
10.30	125	1.005
11	75	1.006
11.30	40	1.008
12 noon	25[2]	–
	1,420	
2 p.m.	60	1.015
4	70	1.016
6	65	1.019
8	60	1.022
7 a.m.[2]	260	1.023
	1,935	

[1] Body weight 71.0 kg.
[2] " " 68.5 " "

Table 30.

J: IV: 6. Water and thirst test. 1,300 cc water given at 7 a.m. and 50 cc at 8 p.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.	110	1.009
8[1]	30	1.007
8.30	200	1.003
9	230	1.001
9.30	195	1.001
10	190	1.002
	845	
10.30	75	1.004
11	90	1.004
11.30	100	1.004
12 noon	70	1.006
	1,180	
2 p.m.	210	1.008
4	220	1.007
6	160	1.009
8	200	1.010
8 a.m.[2]	435	1.014
	2,405	

[1] Body weight 64.5 kg.
[2] „ „ 62.8 „ .

Table 31.

J: IV: 10. Water and thirst test. 950 cc water given at 7 a.m. and 50 cc at 8 p.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	70	1.013
8	125	1.007
8.30	170	1.001
9	210	1.002
9.30	110	1.005
10	50	1.006
	665	
10.30	30	1.008
11	35	1.009
11.30	45	1.010
12 noon	40	1.011
	815	
2 p.m.	130	1.011
4	115	1.011
6	115	1.015
8	85	1.017
8 a.m.[2]	365	1.019
	1,625	

[1] Body weight 39.5 kg.
[2] „ „ 38.4 „ .

Table 32.

K: III: 9. Water and thirst test. 1,500 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	130	1.016
8	490	1.004
8.30	500	1.001
9	450	1.001
9.30	210	1.004
10	110	1.006
	1.760	
10.30	70	1.010
11	80	1.011
11.30	110	1.013
12 noon	60	1.014
	2,080	
2 p.m.	140	1.017
4	120	1.017
6	120	1.021
8	60	1.022
8 a.m.[2]	260	1.028
	2,780	

[1] Body weight 72.1 kg.
[2] " " 69.8 " "

Table 33.

K: IV: 16. Water and thirst test in 10th month of 4th pregnancy. 1,500 cc water given at 7 a.m., 150 cc at 6 p.m. and 150 cc at 8 p.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.	1.000	1.004
8	200	1.003
8.30	75	1.002
9	95	1.002
9.30	450	1.002
10	300	1.002
	1.120	
10.30	650	1.003
11	300	1.005
11.30	100	1.005
12 noon	100	1.007
	2.270	
2 p.m.	800	1.005
4	750	1.004
6	650	1.005
8	600	1.004

Partus after the last portion.

Table 34.

K:IV:16. Water and thirst test 10 months after termination of 4th pregnancy. 1,500 cc water given at 7 a.m., 125 cc at 6 p.m. and 150 cc at 8 p.m. During the test 475 cc milk were pumped from her breasts.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	160	1.005
8	190	1.005
8.30	280	1.003
9	210	1.001
9.30	220	1.002
10	180	1.003
	1,080	
10.30	80	1.004
11	100	1.004
11.30	110	1.004
12 noon	20	1.008
	1,390	
2 p.m.	50	1.010
4	210	1.010
6	130	1.011
8	70	1.015
8 a.m.[2]	350	1.016
	2,200	

[1] Body weight 50.6 kg.
[2] „ „ 49.4 „ .

Table 35.

K: IV: 18. Water and thirst test. 1,500 cc water given at 7 a.m.

Time	*Urine cc*	*Specific gravity*
7 a.m.[1]	120	1.013
8	140	1.003
8.30	310	1.001
9	350	1.000
9.30	230	1.001
10	160	1.001
	1.190	
10.30	85	1.003
11	45	1.006
11.30	25	1.011
12 noon	25	1.011
	1.370	
2 p.m.	45	1.020
4	45	1.021
6	35	1.025
8	25	1.030
7.30 a.m.[2]	130	1.034
	1.650	

[1] Body weight 53.7 kg.
[2] „ „ 53.1 „ .

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